ISSN 2785-9274

PHARMACY BULLETIN

PERMAI

Volume 1/2023
May 2023

Medication Error Reporting:

Underreporting and barriers in reporting medication errors among healthcare professionals

Also in this issue:

Medication Safety:
Updates on:
use of medicines containing animal ingredients

Adverse Drug Reaction:
Tardive dyskinesia

Counselling Points:
Methylphenidate long-acting (modified-release) preparations

Published by
Pharmacy Department, Hospital Permai Johor Bahru

A Message from the Editorial Board

Greetings Dear Readers,

It gives us great pleasure to present Volume 1 of our Pharmacy Bulletin May 2023 issue (ISSN 2785-9274) to you. We present to you a diverse selection of articles from our co-editors and critical appraisal of selected article. In this current issue, we have chosen "Medication Error Reporting: Underreporting and barriers in reporting medication errors among healthcare professionals" as this month's cover story, which we hope will be of interest to you.

We would like to extend our appreciation to the advisor of this bulletin for her support to its publication. We are also beyond grateful to the reviewers for their time and effort in reviewing this publication.

We hope you enjoy reading this bulletin. We welcome any feedback, constructive comments or enquiries you may have on the articles in this publication.

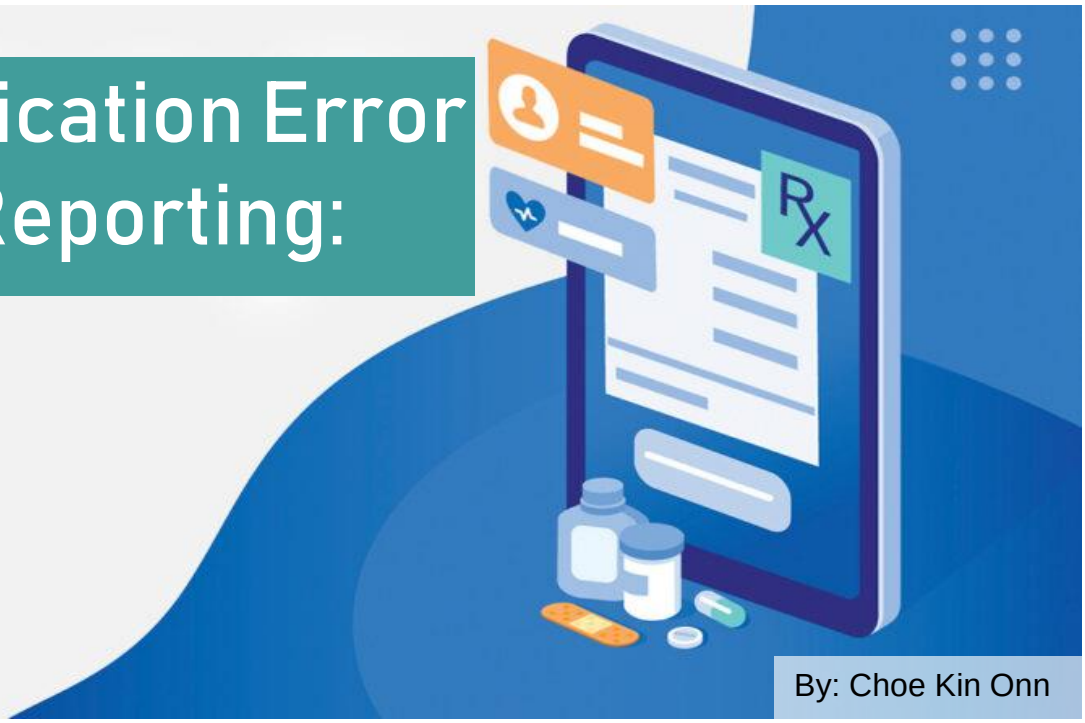
We look forward to seeing you again in the next issue. Happy reading.

The editorial board

Table of Contents

Disclaimer: While every effort has been made to ensure that the information presented in this bulletin is accurate, the editorial board disclaim all responsibilities for any liability, loss or harm incurred as a result of any inaccuracies presented. The content of the bulletin is provided for general informational purposes only and is not intended as, nor should it be considered substitute for professional medical advice. References to particular products or organizations are not a means for endorsement.

Medication Error Reporting:



By: Choe Kin Onn

Underreporting and barriers in reporting medication errors among healthcare professionals

Medication error (ME) is "any preventable event that may cause or lead to inappropriate medication use or patient harm" in the treatment or medication process, including prescribing, dispensing and administration[1]. Actual error is a "medication error occurred and reached the patient" whereas near miss is a "medication error that has the potential to cause an adverse event (patient harm) but did not reach the patient because of chance or because it is intercepted in the medication use process"[1].

The Medication Error Reporting System (MERS) was introduced by the Malaysia Ministry of Health (MOH) in August 2009. MERS is a national reporting system with the primary objective of creating a database on the occurrence of all MEs in the medication management system, of which will be analyzed to establish risk reduction strategies, design policies and develop action plans in order to promote safe medication use in the healthcare system[1].

Medication Error Reporting System
Ministry of Health Malaysia

FAQ: Who can report medication error through MERS?
All healthcare providers from public and private health facilities are encouraged to report medication errors through MERS and share lesson learnt. Example: doctors, pharmacists, dentists, nurses, pharmacist assistants, medical assistants etc.

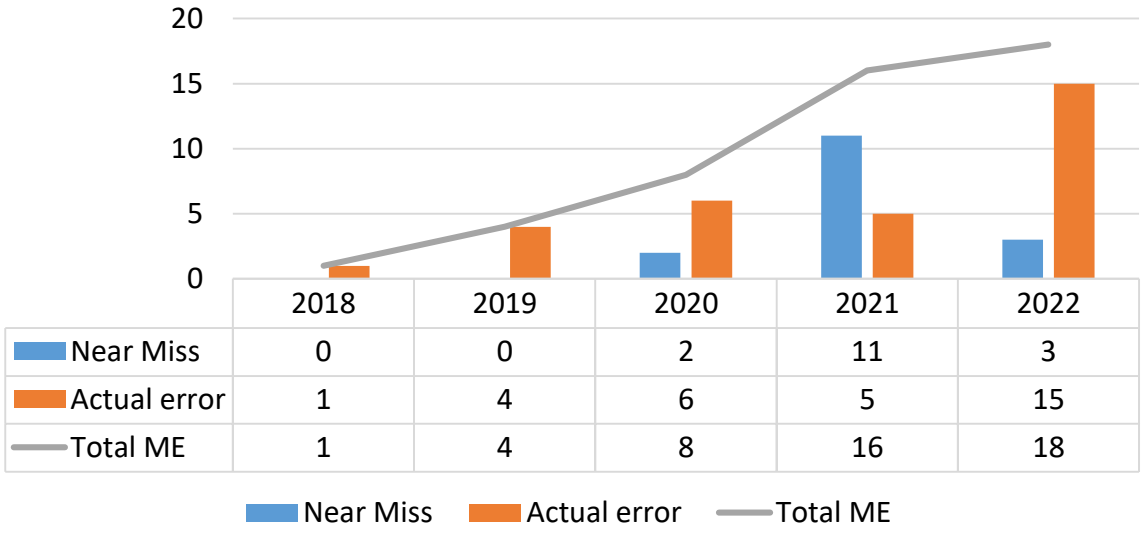
> *Less than half (44.8%) of the respondents who had encountered ME eventually reported them.*

Underreporting of MEs

Underreporting of MEs remains prevalent and has been associated with several barriers to reporting. Analysis of MEs reported to MERS from 2009 to 2012 identified that only 16% of the total errors (*N* = 17,357) were reported by the government clinics[2]. In a survey done in Malaysia, less than half (44.8%) of the respondents who had encountered ME eventually reported them[3]. ME reports were mainly received from hospital pharmacists working in government healthcare facilities compared to doctors[2]. Healthcare professionals are encouraged to provide full details of the ME occurrences in their ME reports to improve the approach in preventing future errors[3]. A study of doctors, nurses and pharmacists of a hospital reported that nurses and pharmacists were more likely to report all types of ME while the doctors were more inclined to report serious errors compared with near misses[5].

Diagram 1 shows the total number of MEs reporting in Hospital Permai from 2018-2022. The uptrend of ME reporting is observed since 2018 likely due to more education and training activities on ME reporting organized regularly.

Diagram 1: Medication Error Reporting Hospital Permai 2018-2022

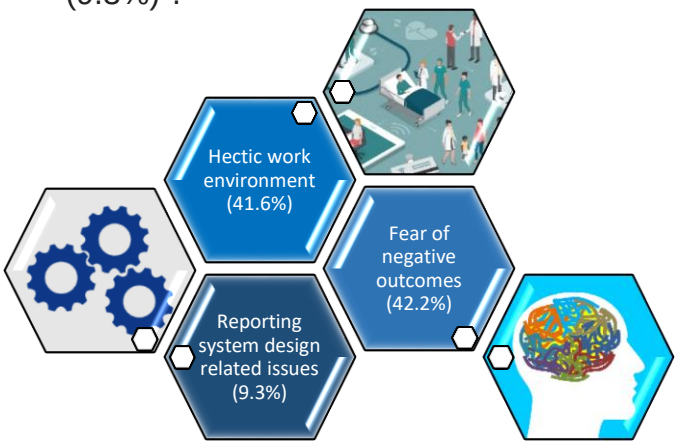


	2018	2019	2020	2021	2022
Near Miss	0	0	2	11	3
Actual error	1	4	6	5	15
Total ME	1	4	8	16	18

However, actual error cases of MEs are highly reported compared to near miss cases in Hospital Permai. According to a qualitative study done in Malaysia, the severity of the error outcome for the patient was the key driver to reporting MEs. [4] Harmful or potentially harmful errors were more likely to be reported than MEs perceived to be harmless[5,8].

Barriers to MEs reporting

In a qualitative study done in Malaysia, the barriers to ME reporting include the reporting system itself which does not guarantee confidentiality of reporter identity, is not simplified, and requires multiple reports[4]. Another survey done in Malaysia categorized hindrances to ME reporting into three factors: hectic work environment (41.6%), fear of negative outcomes (42.2%) and the ME reporting system design-related issues itself (9.3%)[3].



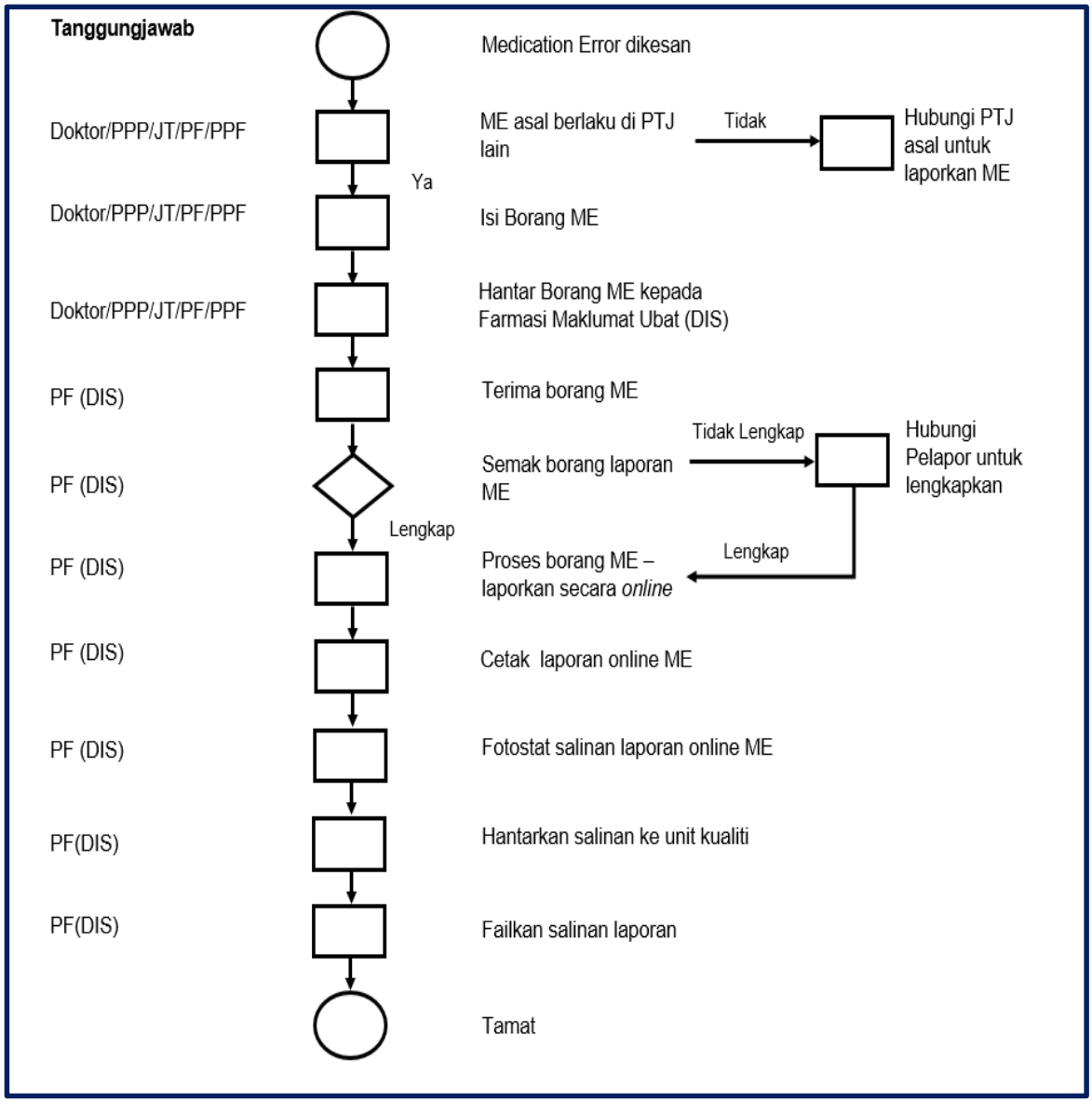
The fear of reporting MEs faced by healthcare professionals was due to possible impending litigation and other punitive actions by governing boards or the facilities' management and losing good working relationships with colleagues. Other reasons for not reporting were the laborious process, busy and hectic work environments and the fact that certain MEs were perceived as being not harmful[5].

Factors facilitating error reporting

Among the factors thought to increase the likelihood of ME reporting include the simplicity of the reporting form, adequate training on the reporting process, anonymity of reporting, adequate feedback received on the reporting, supportive and open working environment[7-8]. A study noted that a clear flowchart should be made visible to guide the reporting process[4]. ME reporting workflow chart of Hospital Permai is distributed to all the wards and units annually to guide healthcare professionals in reporting MEs. ME reporting workflow chart is as shown overleaf:

Workflow chart of Medication Error Reporting

(Pelaporan Kesilapan Pengubatan)



1) **If a Medication Error occurs at another responsible facility (PTJ) but is detected by healthcare professionals in Hospital Permai, then it is necessary to contact the PTJ to report the Medication Error.**
2) **Please complete with as much details as possible in Medication Error form along with Patient Safety Incident Reporting Form and Incident Case Report.**

Way to improve ME reporting

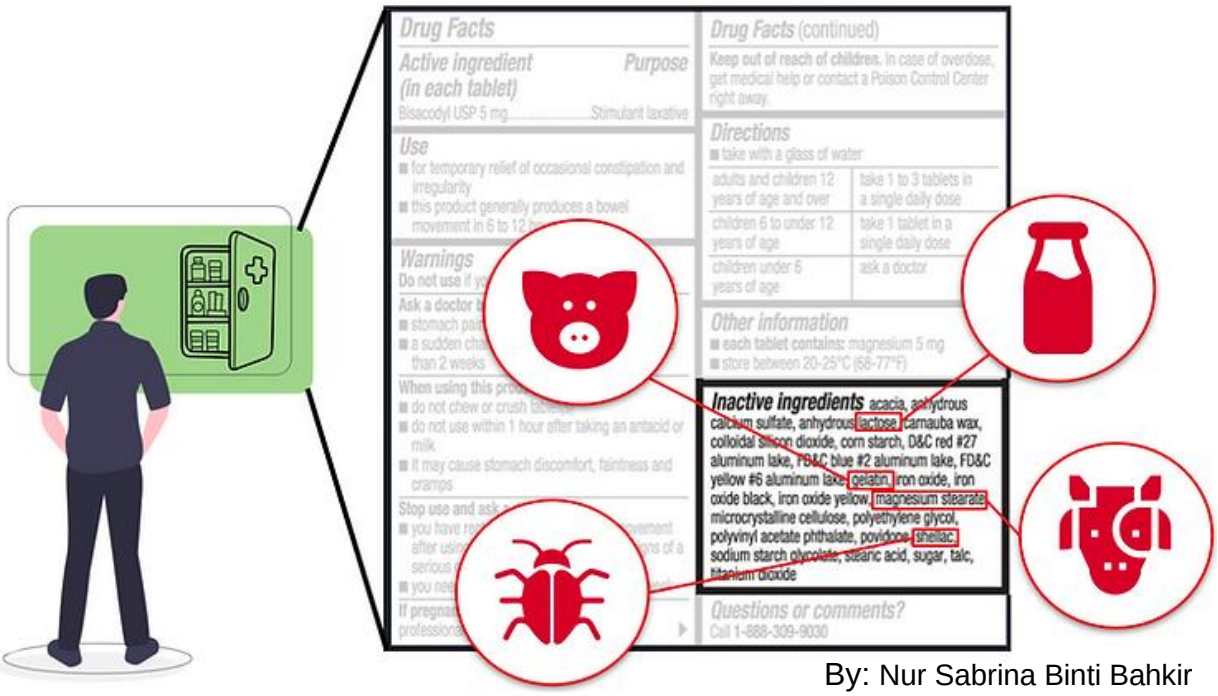
Online ME reporting has been demonstrated to increase reporting rates[6]. Healthcare professionals have found handheld devices such as personal digital assistants to be useful in reporting MEs and adverse events[9]. According to a 2017 survey conducted among doctors and pharmacists in Malaysia, an anonymous smartphone ME reporting application was an acceptable ME reporting method[3]. This reporting method would encourage healthcare professionals to report MEs at the point of which they occurred. Among the features of the smartphone application deemed important to the respondents include user-friendly application, quick, and feedback-enabled[3]. An alternative smartphone ME reporting application could be developed to complement the current ME reporting system to facilitate ME reporting.

Conclusion

The prevalence of underreporting of ME among healthcare professionals remains notable despite continuous efforts on education and training to encourage ME reporting. However, regardless of the method of ME reporting, future efforts could also be focused on designing a holistic intervention plan targeting the multi-faceted components surrounding barriers to underreporting of MEs and to promote and increase self-responsibility and awareness among healthcare professionals in reporting MEs.

References:

1) Guideline On Medication Error Reporting System, Second Edition 2019.
2) Samsiah A, Othman N, Jamshed S, Hassali MA, Wan-Mohaina WM: Medication errors reported to the National Medication Error Reporting System in Malaysia: a 4-year retrospective review (2009 to 2012). Eur J Clin Pharmacol. 2016, 72:1515-1524.10.1007/s00228-016-2126-x
3) George D, Hss AS, Hassali A. Medication Error Reporting: Underreporting and Acceptability of Smartphone Application for Reporting among Health Care Professionals in Perak, Malaysia. Cureus. 2018 Jun 5;10(6):e2746. doi: 10.7759/cureus.2746. PMID: 30087822; PMCID: PMC6075636.
4) Samsiah A, Othman N, Jamshed S, Hassali MA: Perception and attitudes towards medicationerror reporting in primary care clinics: a qualitative study in Malaysia. PLoS One. 2016, 11:e0166114.10.1371/journal.pone.0166114
5) Sarvadikar A, Prescott G, Williams D. Attitudes to reporting medication error among differing healthcare professionals. Eur J Clin Pharmacol. 2010;66:843–53. pmid:2053249
6) Boyer R, McPherson ML, Deshpande G, Smith SW: Improving medication error reporting in hospice care. Am J Hosp Palliat Med. 2009, 26:361-367.10.1177/1049909109335145
7) Hartnell N, MacKinnon N, Sketris I, Fleming M. Identifying, understanding and overcoming barriers to medication error reporting in hospitals: a focus group study. BMJ Qual Saf. 2012;21(5):361–8. pmid:22389018
8) Williams SD, Phipps DL, Ashcroft DM. Understanding the attitudes of hospital pharmacists to reporting medication incidents: a qualitative study. Res Soc Adm Pharm. 2013;9:80–9.
9) Dollarhide AW, Rutledge T, Weinger MB, Dresselhaus TR: Use of a handheld computer application for voluntary medication event reporting by inpatient nurses and physicians. J Gen Intern Med. 2008, 23:418-422.10.1007/s11606-007-0404-0



By: Nur Sabrina Binti Bahkir

Medication Safety: Updates on Use of medicines containing animal ingredients

The gold standard approach in healthcare delivery is person-centered care which has been demonstrated to improve the quality and safety of healthcare, patient outcomes as well as the performance of healthcare services[1]. This includes healthcare professionals taking into consideration patients' religious beliefs and lifestyles when prescribing and dispensing medications.

There are many vaccines, medications and specific medicine formulations such as tablets, capsules, lotion, creams or mixtures which contain animal products or are animal derived. As an example, gelatin is widely used in pharmaceutical industries in making capsule shells and play role as stabilisers in pharmaceutical products such as vaccines. Gelatin is partially hydrolysed collagen which is usually derived from bovine and porcine origin.

Several religions such as the Muslim, Hindu and Buddhist faiths have restrictions on the use or consumption of certain animal-derived products (Table 1)[1]. There is a myriad of opinions on this, and an individual's belief may not necessarily be dictated by their affiliation with a particular religious organization[1]. Hence, healthcare professionals must inform patients regarding the origins of their proposed medication to assist them in making decisions about their treatment. Different group of religions may have their own restriction to grant some exclusion depending of the type of treatment received[1]. Moreover, in the absence of alternative treatment options with similar safety and efficacy profile, and even if the proposed medicine is life-saving, prescribers are required to obtain patient's informed consent of the use of animal or human-derived products.

Religion	Restrictions
Buddhism	Some vegetarian Buddhists, all animal products are prohibited.
Hinduism	Vegetarian: all animal products including egg are prohibited. Non-vegetarian: bovine and porcine containing products are prohibited.
Islam	Porcine and alcohol containing products are prohibited. All animal products that are not killed in the prescribed ritualistic way (*halal*) prohibited.

Table 1: Religious Restrictions

Role and Responsibilities of Prescribers[4]

a) Has knowledge and is aware of the patient's condition.

b) Treatment must be critical and necessary to save the patient.

c) There is no other alternative that can be used and the drug has been clinically proven to be effective and safe to use.

d) The use of the drug is only for a certain period of time order by the Specialist/ Medical Officer.

e) Information must be given to the patient before the medicine is used.

f) Obtain the patient's / guardian's permission first by filling in the patient's consent form.

g) In a life-threatening emergency, the use of the drug is permitted without the patient's prior consent.

Information for Patients before Starting Treatment[4]

Before starting treatment using medicines containing animal elements, prescriber must inform the patient or the patient's carer of the following:-

a) The name of the medicine to be used

b) Indication of the medicine

c) The reason the medicine containing animal elements needs to be used compared to other medicines

The prescriber needs to obtain consent from the patient / patient's next of kin by signing the Patient Consent Form.

Consent Form For Treatment Using Medicine Containing Animal Origin[4]

BORANG KEIZINAN UNTUK MERAWAT MENGGUNAKAN UBAT YANG MENGANDUNGI UNSUR HAIWAN HOSPITAL PERMAI, JOHOR BAHRU

CONSENT FORM FOR TREATMENT USING MEDICINE CONTAINING ANIMAL ORIGIN PERMAI HOSPITAL, JOHOR BAHRU

BIL/*NO.*	NAMA UBAT/*NAME OF MEDICINE*	KANDUNGAN/*ORIGIN*

Saya seperti nama dibawah telah dimaklumkan bahawa *saya/anak/isteri/suami/ibu/bapa perlu menerima rawatan dengan ubat disenarai di atas bagi merawat penyakit saya. Saya faham bahawa ubat ini mengandungi unsur haiwan dalam proses penghasilannya.
*I, as named below, have been informed verbally that *I/my child/my spouse/mother/father need to receive the above listed medicine for the purposes of my treatment. I understand that the medicine mentioned above is derived from animal origin.*

Penerangan yang jelas telah diberikan kepada saya bahawa rawatan ini perlu diberikan kerana tiada alternatif atau alternatif yang ada tidak setara dari segi keberkesanan dan keselamatan.
I have been given clear explanation that this treatment is needed as there are no other alternatives available or the alternatives available are not equal in efficacy and safety.
Oleh itu, saya faham akan penerangan tersebut dan ***bersetuju/tidak bersetuju** untuk menerima ubat yang disarankan.
*Therefore, I understand the explanation given and **agree/disagree** to receive the above mentioned medicine for my treatment.*

Potong yang tidak berkenaan/*Delete where not applicable

Pesakit/Waris
Patient/Next of Kin

……..
Nama & tandatangan/*Name & Signature*:

No Kad Pengenalan/ *Identification Number:*
***Hubungan dengan pesakit /*Relationship to patient:*

Tarikh/*Date:*

Pakar/Pegawai Perubatan
Specialist/Medical Ofiicer

……

Nama & tandatangan/*Name & Signature*:

No Kad Pengenalan/*Identification Number*:

Tarikh/*Date*:

Saksi:
(Diperlukan jika pesakit/waris tidak memahami penerangan yang diberikan oleh doktor)
Witness:
(Required if patient/next of kin cannot understand what is being explained by the doctor)

……

Nama & tandatangan/Name & Signature:

No Kad Pengenalan/Identification Number:

Hubungan dengan pesakit(jika berkenaan)/
Relationship to patient(where applicable):

Tarikh/Date:

List of Medicines with Animal Origin Available in Hospital Permai

No.	Generic Name	Brand Name	Types of Animal Origin	Source of Animal Origin
1	Agomelatine 25mg Tablet	Valdoxan	Bovine	Excipient
2	Alfacalcidol 0.25mcg Capsule*	One-Alpha	Bovine	Capsule
3	Amoxicillin 500mg Capsule	Betamox/Amoxicap	Bovine	Capsule
4	Ampicillin + Sulbactam 375mg Tablet	Unasyn	Bovine	Excipient
5	Asenapine 5mg & 10mg Tablet	Saphris	Bovine	Excipient
6	Atomoxetine HCl 10mg, 18mg, 25mg & 40mg Capsule	Strattera	Bovine	Capsule
7	Calcitriol 0.25mg Capsule*	Osteocap	Bovine	Capsule
8	Cephalexin Monohydrate 250mg Capsule	Pharmaniaga Cephalexin	Bovine	Capsule
9	Cloxacillin 250mg Capsule	Cloxacilla	Bovine	Capsule, Excipient
10	Clozapine 25mg & 100mg Tablet	Clozaril	Bovine	Excipient
11	Doxycycline 100mg Capsule*	Pharmaniaga Doxycycline	Bovine	Capsule
12	Duloxetine 30mg & 60mg Capsule	Cymbalta	Bovine	Capsule
13	Gabapentin 300mg Capsule	Neurontin	Bovine	Capsule
14	Gemfibrozil 300mg Capsule	Pharmaniaga Gemfibrozil	Bovine	Capsule
15	Hydroxyurea 500mg Capsule	DHNP Hydroxyurea	Bovine	Capsule
16	Heparin Sodium 50U in NaCl Injection	Heparinol 10	Bovine	Active ingredient
17	Heparin 5000 U/mL Injection	Heparinol 5000	Bovine	Active ingredient

18	Modified Fluid Gelatin 4% Intravenous Infusion	Infusol SG	Bovine	Active ingredient
19	Mefenamic Acid 250mg Capsule	Pontacid	Bovine	Capsule
20	Methylphenidate 10mg Tablet	Ritalin	Bovine	Excipient
21	Methylphenidate LA 20mg Capsule	Ritalin LA	Bovine	Capsule
22	Olanzapine 5mg & 10mg Orodispersible Tablet	Zyprexa Zydis	Bovine	Excipient
23	Paliperidone 3mg, 6mg & 9mg XR Tablet	Invega	Bovine	Excipient
24	Propofol 10mg/ml (1%) Injection	Propofol Lipuro	Egg	Excipient
25	Phenytoin 100mg Capsule	Dilantin	Bovine	Capsule, Excipient
26	Quetiapine XR 300mg & 400mg Tablet	Seroquel XR	Bovine	Excipient
27	Rifampicin 150mg & 300mg Capsule	Rifampicin Royce	Bovine	Capsule
28	Risperidone 1mg & 2mg Tablet	Rozidal	Bovine	Excipient
29	Ticlopidine 250mg Tablet	Dynapharm	Bovine	Excipient
30	Tramadol 50mg Capsule	Pangesic	Bovine	Capsule
31	Tranexamic Acid 250mg Capsule	Tren	Bovine	Capsule
32	Ziprasidone 40mg & 60mg Capsule**	Zeldox	Bovine	Capsule, Excipient

**** Non-Standard Medicine***
***** Special Approval Medicine***

References:

1) Medicines/pharmaceuticals of Animal Origin V3.0 November 2020. (2021, February 3). *Queensland Health*. https://www.health.qld.gov.au/__data/assets/pdf_file/0024/147507/qh-gdl-954.pdf
2) Medicines with Animal Origin, 1st Edition. HCTM. (2022, July). *HCTM UKM*. https://hctm.ukm.my/farmasi/penerbitan/
3) List of Medicines with Animal Origin: A Practical Guide to Medicines with Animal Origin, 1st Edition (2017). *Hospital Queen Elizabeth*.
4) Garis Panduan Penggunaan Ubat Yang Mengandungi Unsur Haiwan, Edisi Pertama, (2020). Hospital Permai.

By: Ariff Bin Adzahar

Know Your Medication: Olanzapine and Samidorphan

INTRODUCTION[1]

In May 2021, once-daily oral LYBALVI™ (a combination of olanzapine, an atypical antipsychotic, and samidorphan, an opioid antagonist), received first U.S. FDA approval for the treatment of Schizophrenia in adults and Bipolar I disorder in adults (as monotherapy of acute treatment of manic or mixed episodes, as adjunct to lithium or valproate and as monotherapy maintenance treatment).

Olanzapine is a second-generation antipsychotic used in the treatment of schizophrenia and bipolar I disorder. However, use of olanzapine has been associated with weight gain, especially in patients requiring long-term treatment, with impaired metabolism, elevated circulating cholesterol and triglyceride levels being often observed.

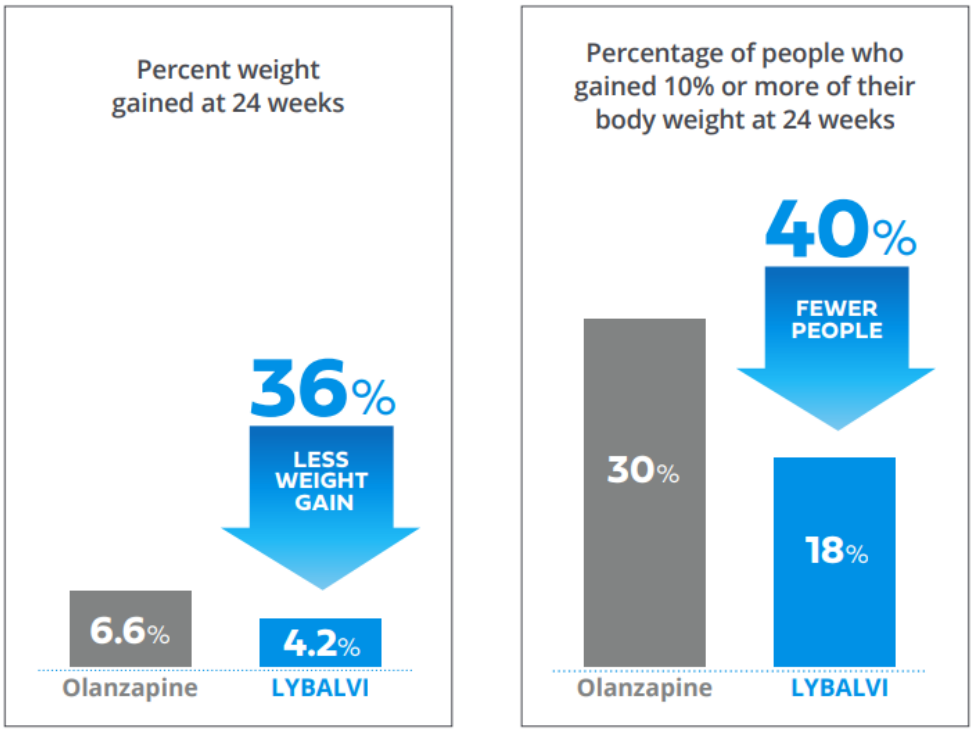
Alkermes Pharma Ireland has developed Samidorphan, a novel opioid receptor antagonist that binds with high affinity to human μ, κ, and δ opioid receptors in vitro and acts as an antagonist of μ-opioid receptors and a partial agonist of κ- and δ-opioid receptors. Samidorphan is formulated with olanzapine as a single-dose oral tablet (LYBALVI™) to reduce the risk of weight gain while providing the therapeutic benefits of olanzapine for the treatment of schizophrenia and bipolar I disorder.

LESS WEIGHT GAIN THAN WITH OLANZAPINE[2]

In a study of adults living with schizophrenia, patients gained less weight with LYBALVI than with olanzapine. The effect of LYBALVI on body weight was studied in a 24-week study that included 538 patients with schizophrenia. 266 patients received LYBALVI and 272 patients received olanzapine

In this study, adults who received LYBALVI gained one-third less weight than adults who received olanzapine.

- LYBALVI patients gained just over 4% of their weight and olanzapine patients gained almost 7% of their weight
- 18% of LYBALVI patients gained 10% or more of their body weight, while 30% of olanzapine patients gained 10% or more of their body weight
- 25% of patients taking LYBALVI reported weight gain as a side effect compared to 36% of patients taking olanzapine.



DOSAGE FORMS AND STRENGTHS[1]

Tablets (olanzapine/samidorphan):

5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg and 20 mg/10 mg

DOSAGE AND ADMINISTRATION[1]

Indication	Recommended Starting Dose (olanzapine/samidorphan)	Recommended Dose (olanzapine/samidorphan)
Schizophrenia	5 mg/10 mg or 10 mg/10 mg	10 mg/10 mg 15 mg/10 mg 20 mg/10 mg
Bipolar I disorder (manic or mixed episodes)	10 mg/10 mg or 15 mg/10 mg	5 mg/10 mg 10 mg/10 mg 15 mg/10 mg 20 mg/10 mg
Bipolar I disorder adjunct to lithium or valproate	10 mg/10 mg	10 mg/10 mg 15 mg/10 mg 20 mg/10 mg

- Administer LYBALVI once daily with or without food.
- Do not divide tablets or combine strengths.
- Recommended starting dosage is 5 mg/10 mg once daily in patients who have a predisposition to hypotensive reactions, have potential for slower metabolism of olanzapine, or may be more pharmacodynamically sensitive to olanzapine.

CONTRAINDICATIONS[1]

1. Patients using opioids.

Examples of opioids that should not be taken with LYBALVI include:

- Buprenorphine-containing products
- Codeine
- Fentanyl
- Heroin and opium (illicit street drugs)
- Hydrocodone-containing products
- Hydromorphone
- Meperidine
- Methadone
- Morphine
- Oliceridine
- Opioid pain medicines
- Oxycodone-containing products
- Tramadol

This list is meant to provide examples and is not a complete list of opioids

2. Patients undergoing acute opioid withdrawal.

* Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from the last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids to avoid precipitation of opioid withdrawal.*

WARNINGS AND PRECAUTIONS[1]

- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia Related Psychosis
- Precipitation of Opioid Withdrawal in Patients who are Dependent on Opioids
- Vulnerability to Life-Threatening Opioid Overdose
- Neuroleptic Malignant Syndrome
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Metabolic Changes (hyperglycemia/diabetes mellitus, dyslipidemia, weight gain.)
- Tardive Dyskinesia
- Orthostatic Hypotension and Syncope
- Leukopenia, Neutropenia, and Agranulocytosis
- Seizures
- Potential for Cognitive and Motor Impairment
- Anticholinergic (Antimuscarinic) Effects
- Hyperprolactinemia

ADVERSE REACTIONS[1]

Most common adverse reactions (incidence ≥5% and at least twice placebo):

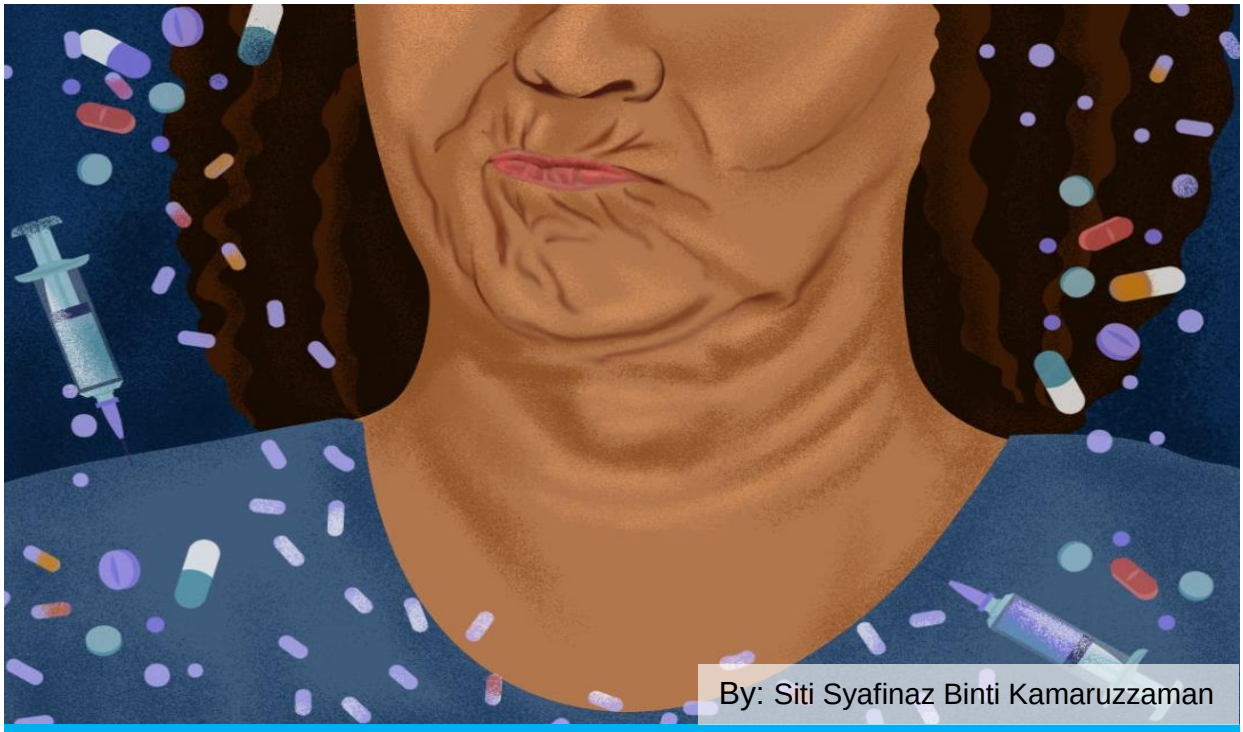
- Schizophrenia: weight increased, somnolence, dry mouth, and headache.
- Bipolar I Disorder, Manic or Mixed Episodes (olanzapine): asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor
- Bipolar I Disorder, Manic or Mixed Episodes, adjunct to Lithium or Valproate (olanzapine): dry mouth, dyspepsia, weight gain, increased appetite, dizziness, constipation, speech disorder, increased salivation, amnesia, paresthesia

USE IN SPECIFIC POPULATIONS[1]

- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates during third trimester exposure.
- Renal Impairment: Not recommended in patients with end-stage renal disease

References:

1) Highlights Of Prescribing Information, LYBALVI™ (olanzapine and samidorphan), 2021. Available from: https://www.lybalvi.com/LYBALVI-Prescribing-Information.pdf
2) Correll, C.U. *et al.* (2020) Effects of olanzapine combined with Samidorphan on weight gain in schizophrenia: A 24-week phase 3 study, *American Journal of Psychiatry*, 177(12), pp. 1168–1178. Available at: https://doi.org/10.1176/appi.ajp.2020.19121279.



By: Siti Syafinaz Binti Kamaruzzaman

Adverse Drug Reaction: Tardive Dyskinesia

Tardive prefix stems from the Latin word "tardus" which means late/slow while dyskinesia means abnormal movement. Tardive dyskinesia is an involuntary neurological disorder and hyperkinetic movement caused by exposure to dopamine receptor blocking agents such as antipsychotics (AP) and antiemetic agents of metoclopramide and prochlorperazine. Tardive dyskinesia (TD) is different from extrapyramidal symptoms (EPS) as TD occurs after months to years of AP administration and persist for at least a month after discontinuation of the causative medications, while EPS occur after initiation of those medications causing the drug need to be discontinue.[1]

MANISFESTATION[1,2]

Oro-bucco-lingual and facial dyskinesia

- Protruding and twisting movements of tongue
- Smacking movement of lips
- Chewing movements
- Blepharospasm – eyelid twitching
- Choreiform hand movements ('piano playing')
- Dystonia and choreoathetoid movements of the limbs

Severe orofacial movements can lead to difficulty speaking, eating or breathing.

RISK FACTORS OF TARDIVE DYSKINESIA[1,2]

Patient	Exposure to dopamine receptor blocking agents	Comorbidities
☐ Older age (over 55 years old) ☐ Female sex ☐ Family history of TD ☐ African American descent 	☐ First generation (FGA) has higher risk than second generation antipsychotics (SGA) ☐ Longer duration of exposure ☐ Higher dose  ☐ Occurrence of extrapyramidal symptoms at early initiation of medication	☐ History of brain damage ☐ Dementia ☐ Intellectual disability ☐ Diabetes ☐ Alcohol or substance use disorder 

PREVENTION[2,3]

1 **Safe prescribing practices**	• Consider the use of second-generation antipsychotics (SGA) than first-generation antipsychotics (FGA) in high-risk individuals • Avoid prolong use of metoclopramide for longer than 12 weeks • Prescribe lowest effective dose and shortest duration
2 **Informed consent and education**	Inform patient about the risk of developing tardive dyskinesia before prescribing with antipsychotic, metoclopramide or prochlorperazine, discuss the alternatives and treatment goals to patients or family
3 **Monitoring during treatment**	Screen the patient for tardive dyskinesia regularly via direct observation or using the Abnormal Involuntary Movement Scale (AIMS) 

MANAGEMENT OF TARDIVE DYSKINESIA[4]

FIRST CHOICE[5]

- Reduce the dose or withdraw antipsychotics
- Withdrawal of any co-prescribed anticholinergic

SECOND CHOICE[5]

- Switch to AP with lower propensity for TD (e.g. clozapine, quetiapine)

THIRD CHOICE[5]

- Valbenazine, tetrabenazine or deutetrabenazine (not available in Malaysia yet)

TREATMENT- ADDITIONAL AGENTS[4]

- Add additional agents instead of reducing or withdraw antipsychotics

Drug	Comments
Amantadine[49–52]	Rarely used but apparently effective at 100–300mg a day
Benzodiazepines[32,33]	Widely used for TD, but Cochrane review considered that the limited evidence for efficacy is inconclusive.[53] Intermittent use may be necessary to avoid tolerance to effects. Most commonly used are clonazepam 1–4mg/day and diazepam 6–25mg/day, with better supporting evidence for the former[36,54]
Deutetrabenazine[8,52,55–57]	Deutetrabenazine (VMAT-2 inhibitor) is also effective as a treatment for TD. Licensed for TD in the USA.[58] Better supporting evidence than for tetrabenazine. Longer half-life than tetrabenazine but still needs to be taken twice a day. Low incidence of psychiatric and neurological effects. Dose is 12–48mg/day
Ginkgo biloba[52,59]	Well tolerated. Cochrane review concluded that while Ginkgo biloba could reduce TD symptoms, the available evidence did not justify its routine use as a treatment.[60] A meta-analysis of three Chinese RCTs showed a good effect with 240mg/day[61]
Pyridoxine[62]	Supported by Cochrane[63] and a meta-analysis.[49] Dose – up to 400mg/day
Tetrabenazine[64,65]	Only licensed treatment for moderate to severe TD in UK. Depression, drowsiness, parkinsonism and akathisia may occur.[54,66] Dose is 25–200mg/day. Reserpine (similar mode of action) also effective but rarely, if ever, used
Valbenazine[8,56,60,67–70]	The evidence supports a favourable benefit-risk ratio for valbenazine (VMAT-2 inhibitor) as a treatment for TD. Licensed for TD in the USA.[71] A dose of 80mg once daily is effective with a benign cardiovascular profile. Low incidence of depression and akathisia
Vitamin E[49,72]	Numerous studies but efficacy remains to be conclusively established. Cochrane suggest that there is evidence only for slowing deterioration of TD.[8,73] Dose is in the range 400–1600 IU/day

Table 1: List of add-on drugs for TD (alphabetical order)

TREATMENT- OTHER POSSIBLE OPTIONS

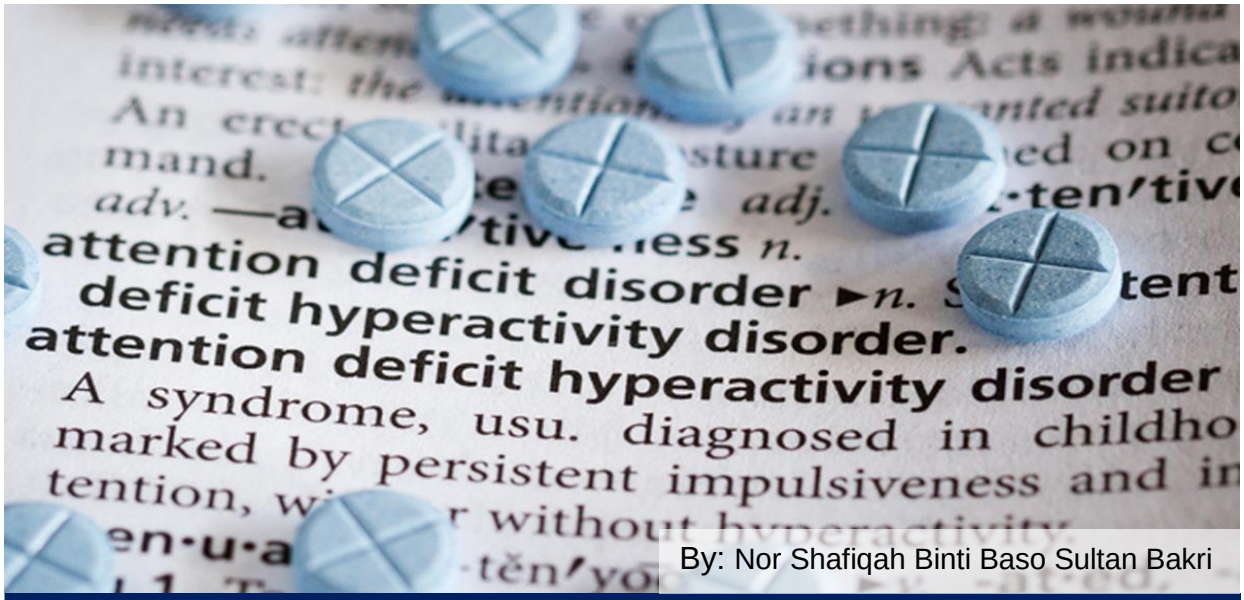
- The large number of possible options indicate the limited effectiveness of standard remedies before the introduction of valbenazine and deutetrabenazine. Table 2 below shows the list of other possible options for TD.

Drug	Comments
Amino acids[74]	Use is supported by a small randomised, placebo-controlled trial. Low risk of toxicity
Botulinum toxin[75–78]	Case reports of success for localised dyskinesia. Probably now treatment of choice for disabling or distressing focal symptoms
Calcium antagonists[79]	A few published studies but not widely used. Cochrane is dismissive.[80] A meta-analysis found no effect[49]
Donepezil[81–83]	Supported by a single open study and case series. One negative RCT (n = 12). Dose is 10mg/day. No clear evidence of efficacy for rivastigmine or galantamine[84]
Fish oils[85,86]	Very limited support for the use of EPA at dose of 2g/day
Fluvoxamine[87]	Three case reports. Dose is 100mg/day. Beware of interactions
Gabapentin[88]	Adds weight to theory that GABAergic mechanisms improve TD. Dose is 900–1200mg/day. Inconclusive data on other GABA agonists[89]
Levetiracetam[90–93]	Three published case studies. One RCT. Dose up to 3000mg/day
Melatonin[94]	Use is supported by a meta-analysis of four trials.[95] Usually well tolerated. Dose is 10mg/day. Some evidence that melatonin receptor genotype determines risk of TD[96]
Naltrexone[97]	May be effective when added to benzodiazepines. Well tolerated. Dose is 200mg/day
Ondansetron[98,99]	Limited evidence but low toxicity. Dose – up to 12mg/day
Propranolol[100–102]	Formerly a relatively widely used treatment. Open-label studies only and a prospective randomized trial is probably warranted. Dose is 40–120mg/day. Beware of contra-indications (asthma, bradycardia, hypotension)
Quercetin[103]	Plant compound which is thought to be an antioxidant. Some promising case reports[103–105]
Sodium oxybate[106]	One case report. Dose was 8g/day
Repetitive transcranial magnetic stimulation (rTMS)[107,108]	RCT data on patients with 'tardive syndromes' suggest the potential for bilateral hemispheric high frequency rTMS to be a feasible treatment where TD is unresponsive to 'first-line' medical treatment[107]
Zolpidem[109]	Three case reports. Dose 10–30mg a day

Table 2: List of other possible options for TD (alphabetical order)

References:

1) Andres Deik, & Daniel Tarsy. Tardive dyskinesia: Definition, etiology, risk factors, clinical features, and diagnosis. UpToDate. Available from: https://www.uptodate.com/contents/tardive-dyskinesia-etiology-risk-factors-clinical-features-and-diagnosis
2) Parna Haghparast, P.D. and Saro Arakelians, P.D. (2022) *Clinical overview: Treatments for tardive dyskinesia*, *Pharmacy Times*. Pharmacy Times. Available at: https://www.pharmacytimes.com/view/clinical-overview-treatments-for-tardive-dyskinesia
3) Liang, T. W., & Daniel Tarsy. Tardive dyskinesia: Prevention, treatment, and prognosis UpToDate. Available from:https://www.uptodate.com/contents/tardive-dyskinesia-prevention-treatment2023-and prognosis?sectionName=PREVENTION&topicRef=4909&anchor=H2&source=see_link#H2
4) David M. Taylor, Thomas R. E. Barnes, Allan H. Young. Management of Tardive Dyskinesia. The Maudsley® Prescribing Guidelines in Psychiatry, 14th Edition, United Kingdom: Wiley Blackwell; 2021. 117p – 119 p.
5) Clinical Practice Guidelines (2021). Management of schizophrenia, 2nd Edition. Ministry of Health, Malaysia. e-ISBN: 978-967-2887-32-4



By: Nor Shafiqah Binti Baso Sultan Bakri

Counselling Points: Methylphenidate long-acting (modified-release) preparations: caution if switching between products due to differences in formulations

In Malaysia, immediate-release and long- acting formulations of methylphenidate are available as oral tablets or capsules. Usually, long-acting formulations are labelled as extended-release, modified-release (MR), long-acting (LA), or sustained-release (SR). The long-acting methylphenidate products available in Malaysia are Concerta, Medikinet MR, and Ritalin LA. Both an immediate-release (IR) and a modified-release (MR) component are present in every long-acting methylphenidate formulation. From there, methylphenidate releases in two stages (biphasic), which enables a quick onset of action and a slower extended release to eliminate the need to take additional dosage throughout the day[2].

All of the brands of LA methylphenidate have different biphasic release characteristics, with variable amounts of the IR and MR components ratio. Long-acting methylphenidate formulations with different time-action profiles allow physicians to target specific parts of the day that are particularly significant for a patient, allowing individualization of ADHD therapy [2].

Changing formulations might cause changes in symptom management during critical times of the day. When long-acting products of different brands are used interchangeably, this may contribute to a change in clinical effect. The same dosage of various products may not produce the same clinical effect[2].

FORMULATION DIFFERENCES

	MEDIKINET MR	CONCERTA ER	RITALIN LA
Dosage form & Strength	Capsules: 5MG, 10MG, 20MG, 30MG, 40MG	Tablet: 18MG, 27MG, 36MG	Capsule: 20MG, 30MG
Ratio of IR and ER	50% : 50% [3].	22% : 78%[3].	50% : 50%[3].
Mechanism of release	Modified-release capsules[3].	OROS® (Osmotic Release Oral System)[3].	SODAS® (Spheroidal Oral Drug Absorption System)[3].
Initial Dose	*New to* methylphenidate: 10mg once daily [5]. Currently using methylphenidate*:* Treatme nt may be continued with the same daily dose [5].	New to methylphenidate: 18 mg once daily for children and adolescents and 18 or 36 mg once daily for adults [6]. Currently using methylphenidate: 18-72 mg [6].	*New to* methylphenidate: 20 mg once daily [7]. Currently using methylphenidate: Treatme nt may be continued with the same daily dose [7].
Onset	20-60 minutes [4].	30 minutes – 2 hours [4].	30 minutes [4].
Tmax	2.75 h [5].	6.8 h [6].	Two strong peaks (early and at 4 hrs) [4].
Excretion	Urine: 78-97% [5]. Faeces: 3% [5].	Urine: 80% [6]	Urine: 78-97% [7]. Faeces: 1-3% [7].
Duration of action	8 hours[4].	12 hours[4].	6–8-hr duration[4].
Their dependence on the presence or absence of food at the time of ingestion	To avoid plasma peaks and to obtain extend effect, MEDIKINET MR must be taken with or after a meal[5].	Bioavailability unaffected by a high-fat meal. Food does not affect dosage dumping. CONCERTA may be administered with or without meals[6].	Bioavailability was unaffected by fasting or a high-fat meal. Presence or absence of food does not cause dosage dumping. Ritalin LA can be taken with or without meals[7].

IR: immediate release; ER: extended release; LA: long acting; MR: modified release

ADVICES ON SWITCHING OF METHYLPHENIDATE

Advice to healthcare professionals[2]:

- Switching preparations may worry patients, parents, and carers. ADHD patients should receive individually-tailored therapy to meet their different requirements.
- Please avoid switching between different products too often.
- If long-acting methylphenidate formulations are used interchangeably, dosage, frequency, meal administration, modified-release component amount and duration, and clinical effect must be considered.

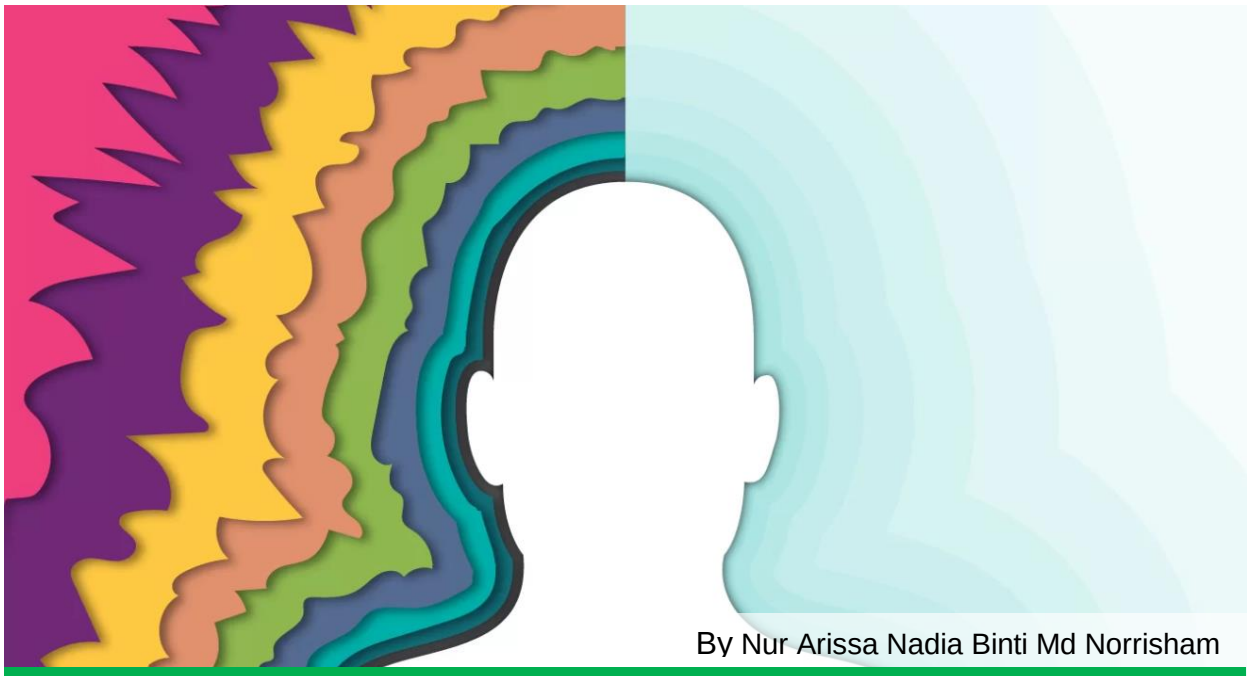
- Follow specific dosage recommendations for each formulation.
- If considering a switch to another long-acting preparation:
  a) Discuss the reasons for considering a transition with the patient (parent or caregiver, if applicable), and any potential changes in symptom management or adverse effects
  b) Consider the patient's wishes in terms of specific requirements, preferred dosing schedule, tolerance for potential adverse effects, and other concerns to the treatment.
  c) Remind the patient of the dosing directions, paying specific attention to whether the newly recommended formulation should be taken with or without meals.
- Recommend prescribing these long-acting methylphenidate formulations by specifying the brand name or by the generic medication name and manufacturer name.
- Clinicians and pharmacists are encouraged to exercise caution when switching patients between long-acting methylphenidate formulations.
- Please report all suspected Adverse Drug Reactions (ADR) while using methylphenidate or any other medication.

Advice to provide to patients or parents and caregivers [2]:

- Long-acting methylphenidate drugs vary in how they release the medication to manage ADHD symptoms and in how they are administered.
- Read and follow Patient Information Leaflet and talk to physician if you are worried about side effects or child's health or medications.
- It's crucial to follow the methylphenidate dosage, timing, and adhere to the instructions to get the most out of your ADHD medication.

References:

1) Use caution if switching between long-acting methylphenidate products due to formulation differences. Available from: https://www.medsafe.govt.nz/profs/PUArticles/March2023/Use-caution-if-switching-between-long-acting-methylphenidate-products.html
2) Methylphenidate long-acting (modified-release) preparations: caution if switching between products due to differences in formulations - GOV.UK. Available from: https://www.gov.uk/drug-safety-update/methylphenidate-long-acting-modified-release-preparations-caution-if-switching-between-products-due-to-differences-in-formulations
3) Coghill D, Banaschewski T, Zuddas A, Pelaz A, Gagliano A, Doepfner M. Long-acting methylphenidate formulations in the treatment of attention-deficit/hyperactivity disorder: a systematic review of head-to-head studies. BMC Psychiatry. (2013,Sep 27). Available from: https://pubmed.ncbi.nlm.nih.gov/24074240/
4) David M. Taylor TREBAHY. The Maudsley® Prescribing Guidelines in Psychiatry. 14th ed. New York, NY: John Wiley & Sons; 2021. 594–595 p.
5) Medikinet MR [package insert on the Internet]. Iserlohn (DE): MEDICE Arzneimittel Pütter GmbH & Co.KG; 2022. Available from: https://quest3plus.bpfk.gov.my/front-end/attachment/3051/pharma/81214/V_60929_20220325_152238_D3.pdf
6) CONCERTA [package insert on the Internet]. Puerto Rico (PR): Janssen Cilag Manufacturing; 2021. Available from: https://quest3plus.bpfk.gov.my/front-end/attachment/44/pharma/210905/V_72602_20221017_171849_D3.pdf
7) Ritalin LA [package insert on the Internet]. Basel (CH): Novartis Pharma AG. Available from: https://quest3plus.bpfk.gov.my/front-end/attachment/17050/pharma/210906/V_66048_20220425_183205_D3.pdf



By Nur Arissa Nadia Binti Md Norrisham

Journal Article Appraisal:
Evaluation of the Safety and Efficacy of Cariprazine in Patients with Bipolar I Depression

Suresh Durgam, M.D., Willie Earley, M.D., et al: An 8-Week Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients with Bipolar I Depression. https://doi.org/10.1176/appi.ajp.2015.15020164	
Background and rationale	The article starts off with the fact that despite manic and hypomanic symptoms are distinguishing characteristic in bipolar mood disorder, depressive episodes being the most disabling and enduring features of the disorder[1] and majority of time spent unwell by bipolar patients accounted for by depressive symptoms[2]. The authors continued to highlights the lack of widely approved and consistently effective treatment for depressive symptoms in bipolar mood disorder having quetiapine and lurasidone are the only FDA-approved antipsychotics for bipolar depression[3, 4]. Cariprazine, a dopamine and serotonin receptor partial agonist with higher affinity and greater selectivity for dopamine D3 than D2 receptors compared to other atypical anti-psychotics[5]. D3 receptors, expressed in brain regions that regulate motivation and reward-related behaviour, may present a new pharmacological target for treating depression[6]. Collectively, the pharmacological profile of Cariprazine suggests potential utility in treating bipolar I depression. The efficacy of Cariprazine in manic or mixed/manic states of bipolar I disorder has been demonstrated in phase II and III clinical trials. In a previous phase II study of Cariprazine in bipolar I depression, improvement compared with placebo did not reach significance on the primary assessment with high placebo response may have contributed to the outcome. The present study further evaluated the efficacy, safety, and tolerability of Cariprazine in bipolar I depression; Cariprazine dosages were selected based on results from the phase II trial (0.75mg/d, 1.5mg/d and 3.0mg/d).

<table>
<tr><td>Objective</td><td colspan="2">To evaluate the efficacy, safety, and tolerability of Cariprazine, in adult patients (18 - 65 years old) with bipolar I depression</td></tr>
<tr><td>Trial design</td><td colspan="2">Double blinded
Both patients and investigator are blind to the allocation, patients continued double-blind treatment through week 8 to assess the persistence of efficacy.
Medications and placebo were delivered in identically appearing capsules.
Placebo-controlled randomized clinical trial
Patients were randomly assigned (1:1:1:1) to receive placebo or Cariprazine at 0.75, 1.5, or 3.0 mg/day by computer-generated numbers for 8 weeks.</td></tr>
<tr><td>Population</td><td colspan="2">A total of 584 patient (18–65 years old) and currently met DSM-IV-TR criteria for bipolar I disorder (confirmed by the Structured Clinical Interview for DSM-IV-TR).</td></tr>
<tr><td>Eligibility</td><td>Inclusion criteria</td><td>Exclusion criteria</td></tr>
<tr><td></td><td>Current major depressive episode without psychotic features that had lasted at least 4 weeks and no more than 12 months)
Total score ≥ 20 on the 17-item Hamilton Depression Rating Scale (HAM-D)
Score ≥ 2 on item 1 of the HAM-D, and a score ≥ 4 on the Clinical Global Impressions severity subscale (CGI-S)
Normal physical examination, vital signs, clinical laboratory test results, and ECG results or abnormal results that were judged not clinically significant.
Negative pregnancy test & use of adequate contraception by women of childbearing potential.</td><td>History or current diagnoses of various axis I disorders other than bipolar I disorder
Concurrent medical conditions that may interfere with study participation, confound interpretation of results, or endanger the patient’s well-being.
Concomitant psychotropic medications prohibited except BZD, Z-drugs, propranolol, diphenhydramine
Hypersensitivity/intolerance to Cariprazine</td></tr>
<tr><td>Intervention / Comparison</td><td colspan="2">Patients were randomly assigned (1:1:1:1) to receive placebo or Cariprazine at 0.75mg, 1.5mg, or 3.0 mg/day as followed:

✓ Day 0: All Cariprazine patient was initiated treatment at 0.5mg/day.
✓ Day 3: Cariprazine dose was increased to 0.75mg/day
✓ Day 5: In the 1.5mg and 3.0mg/d group, dose will be increased to 1mg/d.
✓ Day 8: In the 1.5mg and 3.0mg/d group, dose will be increased to 1.5 mg/d
✓ Day 15: In the 3.0mg/d group only, dose will be increased to 3.0mg/d.
✓ In the subsequent 6 weeks, the dose will be maintained except;
✓ In cases of poor tolerability, patient could be hospitalized during screening and for up to 2 weeks of double-blind treatment.</td></tr>
</table>

Outcome	Primary outcome: • Change in the Montgomery – Asberg Depression Rating Scale (MADRS) from baseline to week 6. Secondary outcomes • Change in the Clinical Global Impression Severity Subscale (CGI-S) from baseline to week 6. • Change from baseline in Hamilton Depression Rating Scale (HAM – D) at week 6 • ≥ 50% score reduction on MADRs • Remission at week 6 with score ≤ 10 on MADRS • HAM – D remitters with score ≤ 7
Statistic	Efficacy analysis: • Based on a modified intention-to-treat population (mITT), which was defined as all patients in the safety population who had at least one MADRS assessment after the start of double-blind treatment (baseline). • All efficacy outcomes assessed using mixed-effects model for repeated measures (MMRM). Safety analyses • Based on the safety population (all randomized patients who took at least one dose of the study drug). Sensitivity analyses: • ANCOVA using the last observation carried forward (LOCF) approach • Pattern-mixture model (PMM).
Results	Primary efficacy outcome: • The use of Cariprazine at 1.5mg/d led to greater least squares mean change from baseline to week 6 in MDRS than placebo. • The least squares mean difference in MADRS score change from baseline to week 6 was statistically significant in favor of Cariprazine at 1.5mg/day compared with placebo (adjusted p = 0.003). Secondary outcome • Use of Cariprazine at 1.5mg/d led to a greater change in CGI-S than placebo The change from baseline was greater & statistically significant (adjusted P = 0.013) for Cariprazine at 1.5mg/d at week 6 until the final follow-up at week 8. • At week 6, Cariprazine at 1.5 mg/day compared with placebo had significantly greater rates of MADRS and HAM-D response, MADRS remission and HAM-D remission. • Cariprazine at 3.0 mg/day was significantly superior to placebo only on MADRS response (p < 0.05).
	Adverse events: • The only adverse events that led to discontinuation in ≥2% of patients were akathisia (3%), agitation (2%), and anxiety (2%) in the Cariprazine 3.0-mg/day group and depression (2%) in the placebo and Cariprazine 0.75 - and 1.5-mg/day groups. • The only serious adverse events considered related to study drug were depression and hypomania (one patient each in the Cariprazine 0.75-mg/day and 1.5-mg/day.

Conclusion	In conclusion, Cariprazine at 1.5 mg/day showed statistically significant improvement on MADRS score and CGI-S change from baseline compared with placebo. Cariprazine was generally well tolerated. Of the Cariprazine dosages studied, 1.5 mg/day demonstrated the most robust efficacy and good safety, suggesting that it may be an effective dosage for the treatment of bipolar I depression. Given the limited number of positive studies for atypical antipsychotics in bipolar I depression, future studies are warranted to extend these phase II findings.
Strength	Strength of the study included the fixed-dosage design, evaluation of three dosages of Cariprazine, prospective remission analyses, and statistical adjustment for multiple comparisons
Limitation	Interpretation of these results is limited by the lack of an active comparator and short treatment duration (8 weeks) The generalizability of findings to patients with psychiatric comorbidities or bipolar II disorder is unclear, since only patients with bipolar I disorder without serious psychiatric comorbidities were enrolled The study was not powered to detect a potential dose response, so it is unknown whether there is a relationship between Cariprazine dosage and therapeutic effect.
Application to clinical practice	Cariprazine is registered but not listed in Drug Formulary MOH. The result may be applied in our local context, yet special drug approval and high cost of drug may limit the usage. Furthermore, the lack of an active comparator and short treatment duration may limit the interpretation of these results. The study also was not sufficiently powered to detect a potential dose response, so it is unknown whether there is a relationship between Cariprazine dosage and therapeutic effect. Therefore, future studies are warranted to extend this phase II finding before they may be utilised.

References:

1) Baldessarini RJ, Vieta E, Calabrese JR, et al: Bipolar depression: overview and commentary. Harv Rev Psychiatry 2010; 18:143–157
2) Baldessarini RJ, Salvatore P, Khalsa HM, et al: Morbidity in 303 first-episode bipolar I disorder patients. Bipolar Disord 2010; 12: 264–270
3) Latuda (package insert). Marlborough, Mass, Sunovion Pharmaceuticals, 2013
4) Seroquel (package insert). Wilmington, Del, AstraZeneca Pharmaceuticals, 2013
5) Kiss B, Horváth A, Némethy Z, et al: Cariprazine (RGH-188), a dopamine D (3) receptor-preferring, D (3)/D (2) dopamine receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. J Pharmacol Exp Ther 2010; 333:328–340
6) LeggioGM,Salomone S, Bucolo C, et al: Dopamine D(3) receptor as a new pharmacological target for the treatment of depression. Eur J Pharmacol 2013; 719:25–33

	QUESTIONS	TRUE	FALSE
1	Actual error is a “medication error occurred and reached the patient” whereas near miss is a “medication error that has the potential to cause an adverse event (patient harm) but did not reach the patient because of chance or because it is intercepted in the medication use process.		
2	In a life-threatening emergency, the prescriber needs to obtain consent from the patient / patient's next of kin for the use of the medicine containing animal origin.		
3	The effect of LYBALVI on body weight was studied in a 24-week study, adults who received LYBALVI gained one-third less weight than adults who received olanzapine.		
4	First-generation antipsychotics (FGAs) have higher incidence of Tardive Dyskinesia than second-generation antipsychotics (SGAs).		
5	Bioavailability of Ritalin LA was affected by fasting or a high-fat meal.		

This page is intentionally left blank

ISSN 2785-9274

This is a publication of the Pharmacy Department, Hospital Permai Johor Bahru.

All enquiries are to be directed to the address below.
Unit Sumber Maklumat Farmasi,
Bahagian Farmasi, Hospital Permai Johor Bahru
Jalan Persiaran Kempas Baru,
81200 Johor Bahru, Johor, Malaysia.
Tel: +607-2311000 (Ext. 1709)
Email: farmasihpermai@moh.gov.my