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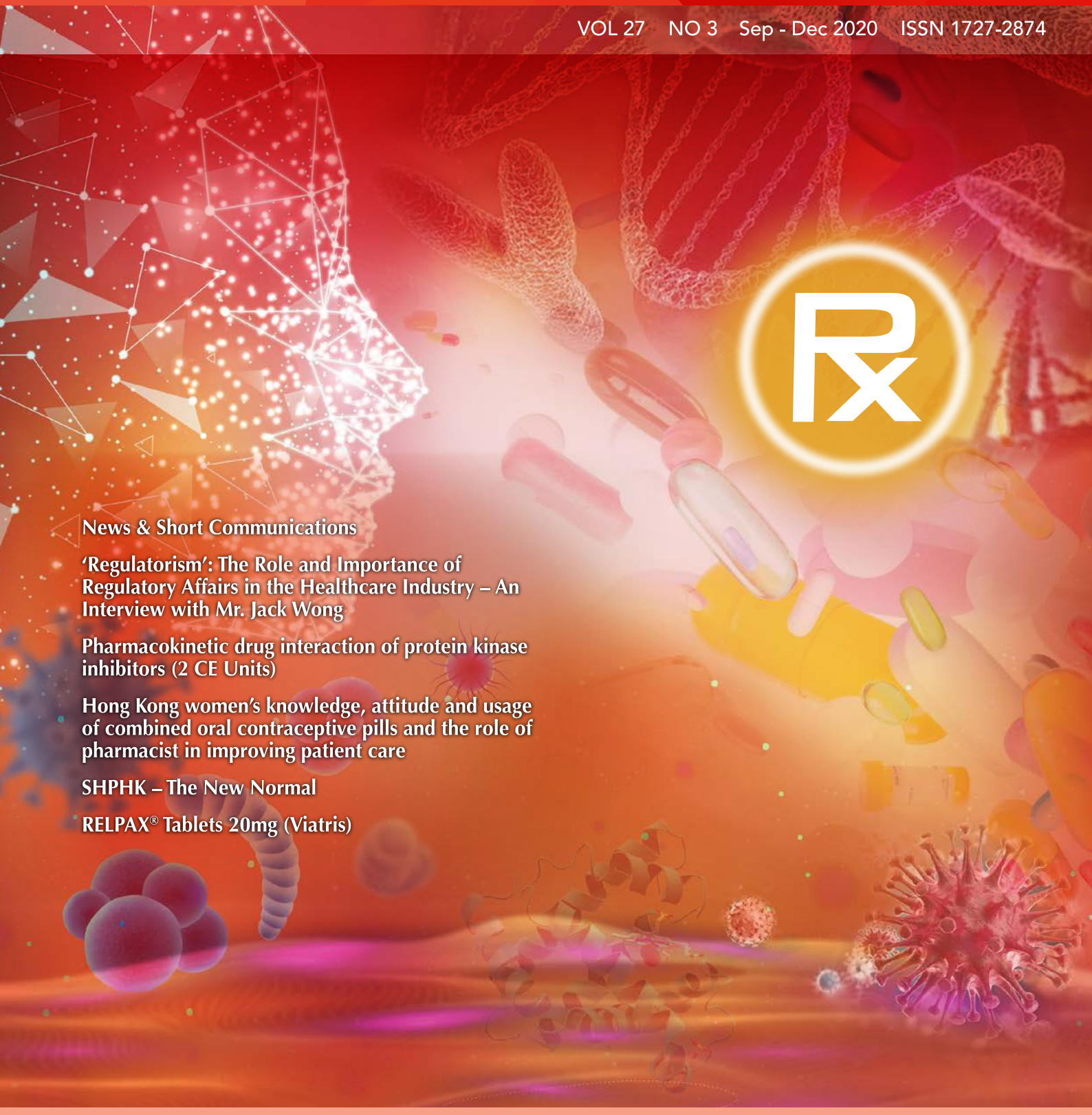

The Pharmaceutical Society of Hong Kong
The Practising Pharmacists Association of Hong Kong
The Society of Hospital Pharmacists of Hong Kong

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All communications and enquiries should be directed to:
The Secretary, Hong Kong Pharmaceutical Journal, Room 1303, Rightful Centre, 12 Tak Hing Street, Jordan, Hong Kong.

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INSTRUCTIONS FOR AUTHORS

The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

- Pharmacy Education & Practice
- Drugs & Therapeutics
- Primary Care
- OTC & Health
- Pharmaceutical Techniques & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
- New Products

Comments on any aspects of the profession are also welcome as Letter to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

e-mail: ***editor@hkpj.org***
address: ***Room 1303, Rightful Centre, 12 Tak Hing Street, Jordan, Hong Kong.***

For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

2020, A Year of Reflection, Resilience and Reawakening

2020 was an exceptional year. The COVID-19 pandemic caught us unaware and unprepared. It has produced unprecedented challenges to both society and to ourselves. Trains and flights were suspended and countries were forced to go into a lockdown. We saw shortages on face mask and hand sanitizier and panic buying and stockpiling of food supplies. We have been physically distanced and learned to meet with friends and family members through computer screens. We put many of our plans on hold due to the heightened fear and uncertainty resulted from COVID-19.

It seems that COVID-19 has moved us into a 'new normal' informed by what we have learnt and experienced. Maintaining social distance and personal hygiene, putting on face masks and carrying hand sanitizers have become standard practice when leaving home. And yet we found hope as we came together with our communities to care for one another. People have demonstrated creativity, resilience, empathy, concerns and care during this difficult time.

In this issue, Mr. Jack Wong (page 72) shared his personal experiences as a pharmacist within the pharmaceutical industry. In this interview, his views on the importance of regulatory affairs in the healthcare industry were discussed. Like many business with digital transformations, Mr. Wong believed that digitalization will be an essential for further advancement in the "new normal" era.

On page 76, Mr. Andy Lam Wai Lok wrote about the drug interaction of protein kinase inhibitors (PKIs). The development of PKIs has reformed oncology practice in recent years. PKIs are used orally, their use is flexible and practical and thereby consequently improving patients' quality of life. Although oral administration is an advantage, chronic use increases the risk of potential drug-drug interaction. This article provided an overview of the mechanisms, clinical effects and recommendations on managing various types of pharmacokinetic drug interactions of PKIs.

The study by Ms. Mandy Lam Yuen Man (page 82) revealed Hong Kong females have knowledge gaps in knowledge, attitude and usage of combined oral contraceptive pills (COCP). As COCP are classified as non-poison by law in Hong Kong and are available over-the-counter, this can be a concern as study showed that misconceptions related to knowledge of COCP were common and there was a low tendency in seeking drug information from healthcare professionals. As suggested by the article, further education and enhanced accessibility to pharmacist service in community is warranted to improve general drug literacy.

I would like to welcome Mr. Kemo Lam, Dr. Ann Leung, Dr. Kiwi Sun and Mr Edward Yau to the Editorial Committee. Last but not the least, I would like to thank all the members of the Editorial Committee for their diligent and dedicated work. They have selflessly contributed their efforts and time in putting together each issue. In addition, my thanks go to all the authors who have been very supportive to the Journal.

As always, you may provide suggestions and give feedbacks on any aspect of the Journal by contacting me or other members of the Editorial Committee. We would very much like to hear your thoughts on any part of the Journal and how we can further develop the Journal. But most importantly, how we can make it more appealing to you, our valued readers.

May PS Lam
Editor-in-Chief
4 January 2021

COMBAT PAIN WITH Celebrex® and Lyrica®

CELEBREX® (CELECOXIB)

Well-tolerated Relief of Nociceptive Pain[1]

22 MINS

Fast onset of pain relief as early as 22 minutes, sustained for up to 24 hours[2]

Fewer upper and lower GI events compared with NSAIDs + PPI[3,4]

Noninferior CV safety compared with ibuprofen or naproxen[5]

First-line Treatment for Neuropathic Pain[6,7]

LYRICA® PREGABALIN

Rapid and sustained pain relief from Day 2[8]

Low potential for pharmacokinetic interactions[7]

Significantly improved pain-related sleep interference and anxiety[9]

Abbreviations: CV=cardiovascular; GI=gastrointestinal; NSAID=non-steroidal anti-inflammatory drug; PPI=proton pump inhibitor

References: 1. Celebrex (celecoxib) Prescribing Information. Pfizer Upjohn Hong Kong Limited: Version May 2019. **2.** Cheung R, Krishnaswami S, Kowalski K. Analgesic efficacy of celecoxib in postoperative oral surgery pain: a single-dose, two-center, randomized, double-blind, active- and placebo-controlled study. *Clin Ther.* 2007;29 Suppl:2498-510. **3.** Chan FKL, Lanas A, Scheiman J, et al. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. *Lancet.* 2010;376(9736):173-9. **4.** Chan FKL, Ching JYL, Tse YK, et al. Gastrointestinal safety of celecoxib versus naproxen in patients with cardiothrombotic diseases and arthritis after upper gastrointestinal bleeding (CONCERN): an industry-independent, double-blind, double-dummy, randomised trial. *Lancet.* 2017;389(10087):2375-82. **5.** Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. *N Engl J Med.* 2016;375(26):2519-29. **6.** Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol.* 2010;17(9):1113-e88. **7.** Lyrica (pregabalin) Prescribing Information. Pfizer Upjohn Hong Kong Limited: Version December 2019. **8.** Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology.* 2003;60(8):1274-83. **9.** Saldaña MT, Navarro A, Pérez C, et al. Patient-reported outcomes in subjects with painful lumbar or cervical radiculopathy treated with pregabalin: evidence from medical practice in primary care settings. *Rheumatol Int.* 2010;30(8):1005-15.

CELEBREX SUMMARY OF PRODUCT INFORMATION 1. TRADE NAME: Celebrex **2. PRESENTATION:** Capsules contain either 100mg, 200mg or 400mg of celecoxib. **3. INDICATIONS:** Adult: For the management of the signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS); management of acute pain (AP) in adults; management of primary dysmenorrhea (PD); treatment of the signs and symptoms of low back pain (LBP). **4. DOSAGE:** OA: 200mg QD or 100mg BID; RA: 100 or 200mg BID; AS: 200mg QD or 100mg BID, 400mg QD if no response after 6 weeks; AP & PD: 400mg initially, an additional 200mg if needed on the first day, subsequent days 200mg BID as needed; LBP: 100mg BID. **5. CONTRAINDICATIONS:** Hypersensitivity to celecoxib, any components of the drug product. Allergic-type reactions to sulfonamides. Experienced asthma, urticaria, or allergy-type reactions after taking aspirin or other NSAIDs. Use as treatment for peri-operative pain in the setting of CABG surgery. Severe heart failure. **6. WARNINGS & PRECAUTIONS:** Increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke. Can cause new onset or worsening of hypertension; Increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine or large intestine; Hepatotoxicity; Heart failure and edema; Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury; Anaphylactic reactions; Exacerbation of asthma related to aspirin sensitivity; Serious skin reactions such as erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN); drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP); Premature closure of the ductus arteriosus; Hematological Toxicity; Masking of inflammation and fever; consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically. **7. INTERACTIONS:** ACE inhibitors and angiotensin receptor blocker, aspirin, beta-blockers, corticosteroids, cyclosporine, diuretics, digoxin; drugs that interfere with hemostasis (e.g. warfarin, aspirin, SSRIs and SNRIs), lithium, methotrexate, NSAIDs and salicylates, pemetrexed and CYP2C9 inhibitors or inducers, CYP2D6 substrates. **8. PREGNANCY AND LACTATION:** Pregnancy Category C; Pregnancy category D from 30 weeks of gestation onward; there are no studies on the effects of Celebrex during labor or delivery. The effects in labor and delivery in pregnant women are unknown. Caution should be exercised when Celebrex is administered to a nursing woman **9. SIDE EFFECTS:** Abdominal pain; Diarrhea, Dyspepsia; Flatulence; Nausea; Back pain; Peripheral edema; Accidental injury; Dizziness; Headache; Insomnia; Pharyngitis; Rhinitis; Sinusitis; Upper respiratory infection; Rash. Reference: HK PI (May 2019) Date of preparation: Mar 2020 Identifier number: CELE0320

LYRICA SUMMARY OF PRODUCT INFORMATION 1. TRADE NAME: LYRICA **2. PRESENTATION:** Each Lyrica hard capsule contains 25mg, 50mg, 75mg, 100mg, 150mg, 200mg or 300mg of pregabalin. (Not all strengths may be marketed). **3. INDICATIONS:** Treatment of peripheral and central neuropathic pain in adults; adjunctive therapy in adults with partial seizures with or without secondary generalisation; treatment of Generalised Anxiety Disorder (GAD) in adults; management of fibromyalgia. **4. DOSAGE:** 150 to 600mg/day given in either two or three divided doses. For neuropathic pain: start at 150mg/day, may be increased to 300mg/day after interval of 3 to 7 days, if needed, to a maximum of 600mg/day after an additional 7-day interval. For epilepsy: start with 150mg/day, may be increased to 300mg/day after 1 week. The maximum dosage of 600mg/day may be achieved after an additional week. For GAD: start with 150mg/day, may be increased to 300mg/day after 1 week. Following an additional week, dosage may be increased to 450mg/day. The maximum dosage of 600mg/day may be achieved after an additional week. For fibromyalgia: The recommended dose is 300 to 450mg/day. Dosing should begin at 75mg BID (150mg/day) and may be increased to 150mg BID (300mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300mg/day may be further increased to 225mg BID (450mg/day). Treatment with doses above 450mg/day is not recommended. Renal impairment: Dosage reduction in patients with compromised renal function must be individualized according to creatinine clearance. Paediatric population: No recommendation on posology can be made. Elderly population: Elderly patients may require a dose reduction due to decreased renal function. **5. CONTRAINDICATIONS:** Hypersensitivity to active substance or to any of the excipients. **6. WARNINGS & PRECAUTIONS:** Some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medicinal products. Hypersensitivity reactions: Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur. Pregabalin treatment has been associated with dizziness and somnolence, and therefore, may influence the ability to drive or use machines. There have been post-marketing reports of loss of consciousness, confusion, mental impairment, visual adverse reactions, and congestive heart failure. Cases of renal failure, misuse, abuse, dependence, encephalopathy, suicidal ideation and behavior have been reported. Withdrawal symptoms have been observed in some patients after discontinuation of short-term and long-term treatment of pregabalin. Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression. Lyrica contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. Please refer to full prescribing information for complete information. **7. INTERACTIONS:** Pregabalin may potentiate the effects of ethanol and lorazepam. **8. PREGNANCY AND BREAST-FEEDING:** There are no adequate data from the use of pregabalin in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Pregabalin should not be used during pregnancy unless clearly necessary. Effective contraception must be used in women of child bearing potential. Pregabalin is excreted into human milk. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy. **9. SIDE EFFECTS:** Very common: Dizziness, somnolence, headache. Common: nasopharyngitis, appetite increased, euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased, ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoesthesia, sedation, balance disorder, lethargy, vision blurred, diplopia, vertigo, vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth, muscle cramp, arthralgia, back pain, pain in limb, cervical spasm, erectile dysfunction, oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue, weight increased. Reference: HK PI (Dec 2019) Date of preparation: Oct 2020 Identifier number: LYRI1020

FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.

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PP-CEL-HKG-0256 Dec 2020

VIATRIS

Prepared by Howard Chan, Chiu TS Ching

Low-Dose Edoxaban Effective for Stroke or Systemic Embolism Prevention in Very Elderly Patients with Atrial Fibrillation

Date: October 29, 2020

Despite guideline recommendations, many physicians are reluctant to prescribe direct oral anticoagulants (DOACs) to very elderly patients with atrial fibrillation (AF) because of perceived bleeding risk factors such as renal failure, previous falls and bleeding history. Lower DOAC doses may be beneficial in patients with high bleeding risk, including very elderly patients, but raise concerns regarding insufficient stroke prevention. The ELDERCARE-AF trial was conducted to examine the efficacy of low-dose edoxaban in very elderly patients with non-valvular AF for prevention of stroke or systemic embolism whom standard DOAC dosing was not recommended.

ELDERCARE-AF was a phase 3, randomized, double-blind, placebo-controlled, event-driven trial which recruited 984 Japanese patients 80 years of age or older with a history of non-valvular AF, $CHADS_2$ score≥2 and were considered to be inappropriate candidates for standard DOAC regimens due to low creatinine clearance (15-30mL/min), history of bleeding from a critical area, low body weight (≤45kg), continuous NSAIDs use, or ongoing antiplatelet treatment. Participants were randomized in 1:1 ratio to receive edoxaban 15mg once daily (n=492) or placebo (n=492). The primary efficacy endpoint was the composite of stroke or systemic embolism, and the primary safety endpoint was major bleeding.

The annualized rate of stroke or systemic embolism was 2.3% in the edoxaban group and 6.7% in the placebo group (hazard ratio [HR], 0.34; 95% confidence interval [CI], 0.19 to 0.61; p<0.001), and the annualized rate of major bleeding was 3.3% in the edoxaban group and 1.8% in the placebo group (HR, 1.87; 95% CI, 0.90 to 3.89; p=0.09). There were substantially more GI bleeding events in the edoxaban group than in the placebo group (HR 2.85; 95% CI 1.03 to 7.88) while no substantial between-group difference in all-cause mortality was observed (edoxaban, 9.9% vs placebo, 10.2%; HR, 0.97; 95% CI, 0.69 to 1.36).

In very elderly Japanese patients with non-valvular AF who were not suitable for standard DOAC doses, 15mg daily edoxaban was superior to placebo in preventing stroke or systemic embolism and did not result in a significantly higher incidence of major bleeding.

Source: www.nejm.org

Daily Low-dose Colchicine Effectively Reduces Cardiovascular Event Risk in Chronic Coronary Disease

Date: Nov 5, 2020

Colchicine, an anti-inflammatory agent commonly used in treating acute gouty attack, exhibits its action by inhibiting tubulin polymerization and altering leukocyte responsiveness. Results of a recent study suggested that low-dose daily colchicine might be effective in reducing risk of cardiovascular events amongst patients with chronic coronary disease.

The LoDoCo2 study was a double-blind, controlled randomized trial investigating the effect of daily low-dose colchicine on reducing cardiovascular event risks. Between August 2014 and December 2018, 5522 patients with well-treated chronic coronary disease (stable background therapy) and tolerated colchicine in the 1-month run-in phase were randomized in 1:1 ratio to receive either colchicine 0.5mg once daily or matching placebo; 5478 received at least one dose of colchicine or placebo. The primary endpoint was a composite of cardiovascular death, non-procedural spontaneous myocardial infarction, ischaemic stroke or ischaemia-driven coronary revascularization.

The date of the last follow-up contact with a patient was February 17, 2020. Study results reflected that low-dose colchicine significantly reduced the occurrence of the primary composite end-point event compared to placebo (number of occurrence, 187 [6.8%] vs 264 [9.6%]; incidence rates per 100 person-years, 2.5 vs 3.6 [HR, 0.69; 95% CI, 0.57 to 0.83; p<0.001]). For secondary end-point events, while low-dose colchicine demonstrated significant effects on most cardiovascular-related parameters such as spontaneous myocardial infarction and ischaemia-driven coronary revascularization, it did not result in a lower incidence of death from any cause than placebo (73 vs 60 fatalities; incidence per 100 person-years, 0.9 vs 0.8 events [HR, 1.21; 95% CI, 0.86 to 1.71]). The individual causes of death were mixed and limits accurate interpretation.

Given the significant effects of low-dose colchicine demonstrated in the study, the medication may potentially be effective in reducing risk of cardiovascular events in chronic coronary disease, though its safety warrants further investigation.

Source: www.nejm.org

Golimumab Potentially Improves Endogenous Insulin Production in Youth with New-onset Type 1 Diabetes Mellitus

Date: November 19, 2020

Type 1 diabetes mellitus (T1DM), an autoimmune disease, leads to progressive pancreatic beta cell loss and research suggests that tumour necrosis factor (TNF)-α appears to play a role in disease development. A recent phase 2 trial suggested that golimumab, a TNF-α inhibitor, may be beneficial in T1DM treatment.

In this double-blind, placebo-controlled, parallel-group randomized trial, 84 patients aged between 6 and 21 years were recruited and underwent randomization in 2:1 ratio to receive either golimumab (weight <45kg, 60mg/m^2 SC at weeks and 0 and 2, then maintenance 30mg/m^2 at week 4 and every 2 weeks through week 52; weight ≥45kg, 100mg SC at weeks 0 and 2, then maintenance 50mg at week 4 and every 2 weeks through week 52) or placebo. The target HbA1c was <7.5% for patients aged less than 18 while for those aged 18 or above the goal was <7%. The primary endpoint was endogenous insulin production, as assessed according to the 4-hour C-peptide AUC at week 52; prior to randomization, all patients had a peak level of ≥0.2pmol/mL after a 4-hour mixed-meal tolerance test. Safety endpoints included adverse events occurred during treatment and hypoglycaemia.

Over 52 weeks, the mean change from baseline in the 4-hour C-peptide AUC was -0.13pmol/mL (12% decrease; 95% CI, -0.23 to -0.03) and -0.49pmol/mL (56% decrease; 95% CI, -0.66 to -0.32) in the golimumab and placebo groups respectively, with a between-group difference being observed as early as week 12. Least-squares mean (+/-SD) HbA1c level achieved was similar between two groups (golimumab, 0.47+/-0.21% vs placebo, 0.56+/-0.29%; p=0.8), while the use of insulin was significantly reduced in the golimumab group (0.07U/kg/day vs 0.24U/kg/day, p=0.001). Hypoglycaemic episodes were similar across groups; notable safety events specific to golimumab were mainly changes in neutrophil count, of which were generally consistent with previously used golimumab regimens.

Golimumab is a human IgG1-κ monoclonal antibody approved for the treatment of various autoimmune diseases, for instance ankylosing spondylitis, rheumatoid arthritis and polyarticular juvenile idiopathic arthritis in children aged 2 years or above.

Source: www.nejm.org

Febuxostat Non-inferior to Allopurinol in Occurrence of Major Cardiovascular Events

Date: November 28, 2020

Initial clinical trials comparing febuxostat to allopurinol or placebo identified a numerically higher risk of cardiovascular events in patients taking febuxostat, whilst subsequent trials showed equal frequencies of adjudicated cardiovascular events. Due to lingering concerns about the possibility of increased cardiovascular risk with febuxostat, the European Medicines Agency (EMA) mandated a post-authorization cardiovascular safety study to evaluate the cardiovascular effect of febuxostat versus allopurinol.

FAST was a prospective, randomized, open-label, blinded-endpoint multicenter trial recruiting patients 60 years or older who had at least one additional cardiovascular risk factor and already receiving allopurinol. Patients who had MI or stroke in the previous 6 months, severe congestive heart failure or severe renal impairment were excluded. After a lead-in phase in which allopurinol dose was optimized to achieve serum urate concentration <6mg/dL, patients were randomly assigned in 1:1 ratio to continue allopurinol at optimized dose or start febuxostat at 80mg/day, increasing to 120mg/day if necessary to achieve the target serum concentration. The primary outcome was a composite of hospitalization for non-fatal MI or biomarker-positive ACS; non-fatal stroke; or cardiovascular death.

6128 patients were recruited with 3065 patients receiving allopurinol and 3063 patients receiving febuxostat. For incidence of the primary endpoint, on-treatment, febuxostat (1.72events/100patient-years) was non-inferior to allopurinol (2.05events/100patient-years) (adjusted HR, 0.85 [95% CI, 0.70 to 1.03; p<0.0001]). All-cause mortality rate was 1.06events/100patient-years in the febuxostat group and 1.44events/100patient-years in the allopurinol group (HR, 0.75 [95% CI, 0.59 to 0.95; p<0.0001]). 57.3% patients in the febuxostat group and 59.4% patients in the allopurinol group experienced at least one severe adverse event (difference, 2.1% [95% CI, −0.4 to 4.6]).

Febuxostat is non-inferior to allopurinol with respect to the primary cardiovascular endpoint; its long-term use is not associated with an increased risk of death or serious adverse events compared with allopurinol.

Source: www.thelancet.com

Finerenone Treatment Lowers Risks of Chronic Kidney Disease Progression and Cardiovascular Events in Type 2 Diabetes

Date: December 3, 2020

Evidence supports the pathophysiological role for mineralocorticoid receptor overactivation in cardiorenal diseases, including chronic kidney disease (CKD) and diabetes, through inflammation and fibrosis leading to progressive organ dysfunction. Finerenone, a nonsteroidal selective mineralocorticoid receptor antagonist, was shown to reduce the urinary albumin-to-creatinine ratio in patients with CKD taking a renin-angiotensin system blocker, while having smaller effects on serum potassium levels than spironolactone. The FIDELIO-DKD trial was conducted to test the hypothesis that finerenone slows CKD progression and reduces cardiovascular morbidity and mortality among patients with advanced CKD and type 2 diabetes.

In this phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial, adults with type 2 diabetes and CKD were treated with a renin-angiotensin system blocker at the maximum dose specified on the manufacturers' labels. Participants were randomly assigned in 1:1 ratio to receive oral finerenone or placebo; patients with eGFR 25-<60mL/min/1.73m^2 received an initial 10mg daily dose, while those with eGFR>60mL/min/1.73m^2 received an initial 20mg daily dose. Dose increase from 10mg to 20mg daily was encouraged after 1 month if serum K^+ level was ≤4.8 mmol/L or less and eGFR was stable. The primary outcome was a composite of kidney failure, a sustained eGFR decrease of ≥40% from baseline over 4 weeks, or death from renal causes. The key secondary outcome was a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or heart failure hospitalization.

5734 patients were recruited into the trial where 2833 patients received finerenone and 2841 patients received placebo. 504 (17.8%) patients in the finerenone group and 600 (21.1%) in the placebo group experienced a primary outcome event (HR, 0.82; 95% CI, 0.73 to 0.93; p=0.001). 367 (13.0%) and 420 (14.8%) patients in respective groups experienced a key secondary outcome event (HR, 0.86; 95% CI, 0.75 to 0.99; p=0.03). Overall, the frequency of adverse events was similar between two groups.

In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo.

Source: www.nejm.org

Government Clarifies Rumours on Internet Regarding Procurement of Mainland Vaccines

Date: December 15, 2020

The Government has earlier made an announcement in September this year that it would adopt a "two-pronged" strategy to procure vaccines for protecting against COVID-19 for the entire Hong Kong population. The Government has on one hand joined the COVAX Facility led by the World Health Organization (WHO), and at the same time directly entered into advance purchase agreements with individual vaccine developers for obtaining greater supplies of vaccines at an earlier time.

As indicated by information by the WHO in the public domain, COVID-19 vaccines are mainly developed from four different technology platforms, including inactivated, viral vector, nucleic acid and protein subunit. The Government has consulted the Joint Scientific Committee on Emerging and Zoonotic Diseases and the Scientific Committee on Vaccine Preventable Diseases under the Department of Health and the Government's four experts on anti-epidemic efforts regarding the above technology platforms and the candidate vaccines from each of the technology platforms which have basically entered into phase 3 clinical trial. The experts took the view that each technology platform has its merits. The experts also understood that the Government should procure candidate vaccines developed from different vaccine manufacturers and from different technology platforms. It should also procure sufficient doses to cover for at least two times the Hong Kong population, with a view to diversifying risks and ensuring sufficient supplies of vaccines for the whole of Hong Kong.

The developers/manufacturers of the three vaccines now purchased by the Government are respectively Sinovac Biotech (Hong Kong) Limited (inactivated virus vaccine), Fosun Pharma/German drug developer BioNTech (nucleic acid vaccine) and AstraZeneca/University of Oxford (viral vector vaccine). These vaccines are frontrunners in terms of the progress of scientific research and technology development and clinical trials from the three respective technology platforms. The Government's decision on procurement of the relevant vaccines is reached after having made reference to the experts' views on candidate vaccines and having considered factors such as the quantity and timing of supply, logistics and storage methods, etc. The decision on procurement of vaccines is made based on the considerations of safety, efficacy, quality and supply, and does not in any way involve political factors.

https://www.info.gov.hk/gia/general/202012/15/P2020121500015.htm

'Regulatorism': The Role and Importance of Regulatory Affairs in the Healthcare Industry – An Interview with Mr. Jack Wong

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ABSTRACT

In this interview, Mr. Jack Wong shares his personal experiences as a pharmacist within the pharmaceutical industry and his views on the importance and future of regulatory affairs in the healthcare industry.

Keywords: *Regulatory Affairs, Regulatorism, Healthcare Industry, Pharmaceutical Companies, Digitalization*

INTRODUCTION TO MR. JACK WONG

Mr. Wong is currently the Associate Vice President of Regulatory Affairs (Asia Pacific, Middle East, and Africa) at Allergen. He graduated from the University of Brighton with a pharmacy degree in 1995. With a strong passion for Regulatory Affairs (RA), he spent over 20 years being a part of multiple pharmaceutical companies – namely Johnson & Johnson, Terumo BCT and Baxter International Inc as the Director and Head of RA. Within these companies, he pioneered training programs for regulators within the region and received awards for initiating projects to align all product launching processes.

He is currently a guest lecturer for RA modules at the University of Sydney, University of Hong Kong, Chinese University of Hong Kong and Tohoku University in Japan where he shares his views on the importance of RA within the healthcare and pharmaceutical industry.

He is the Executive Deputy Secretary General in the Asian Harmonization Working Party (AHWP) which facilitates Health Authorities and industries to enhance regulatory competency in Asia. In 2007, he developed the first Asia Regulatory Affairs Certificate course which has trained over 2800 individuals within the pharmaceutical industry, the government, and universities.

In 2010, he founded the Asia Regulatory Professional Associations (ARPA) and wrote the Handbook of Medical Device Regulatory Affairs in Asia (2nd Edition).

THE INTERVIEW

Q: What is Regulatory Affairs to you?

Mr. Wong: To me, RA is very meaningful and critical within the healthcare industry. The healthcare industry is highly regulated. There are regulations related to clinical trials, product registration, importation, product label content, promotional claims, adverse event reporting etc. RA professionals have critical roles to monitor and ensure compliance.

RA professionals also have a big impact on patients' lives, as innovative or improved products will not be available for patients without product registration approval.

Q: What is the most difficult part of the job?

Mr. Wong: The most difficult part of the job as a Regulatory Affairs Executive is to manage the external and internal communications.

Internal communication challenges occur within the company. When a product registration needs to be done, constant communication and work prioritization are required not only within your team, but also with other members from the marketing team, the manufacturing and production team, and the supply chain team.

With the marketing team, issues regarding the project priority, product claims and package size must be discussed thoroughly. With the manufacturing and supply team, constant and effective communication must occur to ensure that production will be completed on schedule for the targeted market. Whereas with the supply chain team, it is important to discuss when the product will be available for launch and explore ways to save time for a quicker product launch.

Prioritizing work as an RA executive is difficult especially when so many teams are involved in the process. As an executive, I must communicate effectively with my regional and global colleagues, as everyone may have their own angle or opinion regarding product prioritization, and which products should be supplied for a specific region. The impact on patients, business potential, and speed to market are common criteria considered during prioritization communication.

Externally, I would say communication with regulators and government agencies is challenging. We need to ensure our documentation meets the demanding and dynamic requirements. We also need to explain the science and technology of our products to assist government review. Sometimes, we need to negotiate with the government, keeping in mind the efficacy, safety, and quality of the product. Some companies push for a quicker review because they want to increase product sales, however, this is a common mistake as the government's main focuses are efficacy, safety, and quality of the product – not the company's sales.

Q: Are there any major differences or changes in the present role of a RA pharmacist compared to the past?

Mr. Wong: There is, without a doubt, a huge shift in the role of a pharmacist from the past compared to the present. The main change would be the shift from administrative work to more strategic planning.

In the past, RA pharmacists were only required to submit applications, follow up with the applications and get approvals for products. But nowadays, more and more RA pharmacists are taking part in strategic planning by proposing different paths for registration based on the customer's business strategy. This is because the same product can have different descriptions that can affect its registration path.

An example is alcohol wipes, which can be registered in 3 different ways. The first is to register it as a pharmaceutical product used to clean wounds, as it has a clear pharmacological action. The second is to register it as a medical device, as it can be used to clean surgical instruments. The third is to sell the product as a household product in the supermarket with no medical use and pharmacological action, as it can be used to clean household items.

Q: You received awards for your outstanding performance in reducing product launch time. Can you briefly explain the processes prior to product launching?

Mr. Wong: At every company I work at, I launch "Project 20%" to reduce overall product launch time by 20%.

There are two steps that must be ensured prior to product launching. The first is to align all the departments that are involved in the product launching process, such as the regulatory affairs team, the supply chain, and the commercial team. By aligning all the departments, we can clearly identify the responsibilities and roles of each department throughout the entire process. The alignment process is typically not difficult, as each department knows their own responsibilities.

Awards from Allergan Pharmaceuticals and Baxter International Inc. for reducing product launch times

The second step is to create transparency by having all teams communicate with each other often regarding the project launch milestones. This is done by having a mechanism in place to review the timetable regularly together, so that the timetable can be adjusted based on the progress of each team. Transparency can lead to streamlining, where we can identify which steps can start earlier, or happen in parallel – ultimately saving a lot of time throughout the entire process.

Both steps create an easy winning formula. There are a lot of companies that cannot achieve transparency and streamlining, which makes it difficult for them to shorten the amount of time required for product launching.

Q: What about the training programs you developed at the British Standard Institute? What was the purpose and what did these programs mainly focus on?

Mr. Wong: During my time at the British Standard Institute, I noticed a few issues. The first is that the supply of people working in Regulatory Affairs is limited. There is no designated university course to train or educate individuals to become RA professionals, whilst the demand for such professionals keep increasing. In addition, the amount of work required for registering products keep increasing, and regulation guidelines around the world keep getting tougher.

The second issue is that not many people know about the role and the importance of RA in pharmaceutical or MedTech companies. So, the main goal of the training programs I developed is to help increase supply of RA professionals by creating awareness of RA, and by increasing professionalism of RA professionals through training.

Q: You founded the Asia Regulatory Professional Association in 2010. What prompted this and what is the purpose of the Association?

The Asia Regulatory Professionals Association (ARPA) was established in 2010, with the aim to raise the standard and social recognition of Regulatory Professionals.

Website: https://ARPAedu.com

Mr. Wong: The purpose of ARPA is to raise awareness of the importance of RA in the healthcare industry. This is primarily achieved by training professionals, publishing textbooks, and creating forums for the government and industry professionals to meet regularly and share their practice.

Q: What are some achievements of the Asia Regulatory Professional Association?

Mr. Wong: There are many achievements of the ARPA. The first would be the successful introduction of RA certificate courses in 9 universities around Asia, and the provision of training courses to regulators, government officials and organizations in more than 5 countries to improve professionalism.

The second would be creating forums for professionals to share their practices, which allows for regular communication between the government and the industry professionals.

Regulatory forum in Hong Kong, 2020

The third would be the release of two major publications regarding our training, which aims to share good practice in the regulatory field.

The ARPA is actively looking for contributors!

If you are interested in being a student, a speaker, writer, or participant in forums, please do not hesitate to contact Mr. Wong at: **JackWong@ARPAedu.com**

Q: What is the Asia Regulatory Professional Association developing or working on currently?

Mr. Wong: We are currently working hard to expand the number of certified courses offered in universities around Asia.

The ARPAedu website is going to be launched this year, which aims to provide more online education and tools to support regulatory professionals.

Q: You mentioned that the demand for RA professionals is increasing, whilst there is still insufficient supply. In your opinion, what can be done to increase regulatory manpower?

Mr. Wong: Organizing regulatory training is an option but training alone will never be enough to supply the demand.

Every company within the pharmaceutical or MedTech industry should have RA professionals, as it is a highly regulated environment. However, small companies are often unable to recruit someone to work there as a RA officer or executive.

Often, small companies end up trying to go through with the entire process themselves through trial and error, which is time-consuming, and difficult. This is where the ARPAedu website we are developing at ARPA comes in.

The aim of the website is to provide training, databases, networks and platforms for different service providers to support RA work in small companies.

Q: You introduced the idea of "Regulatorism" in an article recently. What is "Regulatorism"?

Mr. Wong: "Regulatorism" means that all healthcare companies, including smaller companies, should have strong regulatory competence.

Q: What are the important steps companies or industry executives should take to achieve this?

Mr. Wong: The concept of "Regulatorism" is straightforward, but achieving it is difficult.

Normally, step one is to ensure that the senior management buys in. The boss of the company must agree to improve regulatory competence.

Ideally, the second step is to recruit RA professionals. If the company is unable to do so, then they should try to allocate resources to build up competency – either by sending someone or a team of people to go for training, or to use the tools we are developing at ARPA.

The third and fourth step is execution, and measurement. Senior management should review the feedback and outcomes. Based on the outcomes and feedback received, senior management should aim to make changes to address any issues. After a few cycles of this, the company will be able to achieve strong regulatory competency.

Q: What are some difficulties that companies may encounter when they are on the path to "Regulatorism"? How can they overcome this?

Mr. Wong: The number one difficulty is obtaining senior management buy-in, as they might not be clear on what RA is. Thus, I believe gaining their understanding and buy in is the main difficulty.

The second difficulty would be acquiring and allocating resources, as this step often requires a lot of money, or discussion regarding which individuals should be sent for RA training.

Q: What do you think will be the next step for RA within the healthcare and pharmaceutical industry?

Mr. Wong: Personally, I think that digitalization will be the next big step. Covid-19 has had a huge impact on the whole world, not just the economy. In the past, people think that face-to-face conferencing is the best option, whereas now everything is conducted online. I believe that this will speed up the new digitalization phase of RA.

Q: What have you done in the past that you are proud of?

Mr. Wong: I am proud of all my achievements, especially with Project 20%, a project that saves 20% product launch time, and the founding of ARPA.

I am also proud of my personal achievements outside of work – namely the Boots Prize Award for the highest examination results in pharmacy school, and when I won the interuniversity table tennis competition in the U.K.

I try to balance my life from different aspects, rather than just working and focusing on one thing. I believe that it helps me enjoy life a lot more.

Q: What are you planning on working on next?

Mr. Wong: Currently, my next step is to launch the ARPAedu website this year and explore more digitalization and Artificial Intelligence tools to help RA.

I have also been working on a side project, Rise Beyond, which involves the training of handicapped individuals to work in RA and start their own regulatory consultancy company in Hong Kong. Although this is not a primary direction of ARPA, I believe that it is important to utilize your knowledge to do something meaningful for others as well. If the model of this side project works, I would like to expand the model to other Asian countries as well.

Q: You have been working in the RA industry for a long time. Is there anyone that you look up to?

Mr. Wong: I really look up to Steve Jobs for his creativity, and Jack Ma for his boldness. As an English teacher, Jack Ma did not know much about the internet in China. Yet, he just gathered a team and started to figure it out with passion. Both of these individuals taught me to take initiative and do what you want to do to achieve your hopes and dreams.

Q: How can young pharmacists or pharmacy students prepare themselves if they are interested in working in the RA industry? Are there some tips you would like to offer aspiring or young pharmacists?

Mr. Wong: Learn the regulatory requirements and principles. Build networks within the government and the industry. Identify clerkship opportunities to handle RA products and understand how different departments work together. For example, as a pharmacist, you may feel as though you do not need to learn and understand how the supply chain works. However, you might find it fun to learn as you can gain various transferable skills (e.g. product management, product tracking, supply alert), which can be used in RA.

Work life balance is critical as well, it is important to enjoy your personal life outside of work or education!

CONCLUSION

With increasingly tough regulations for medical product registration, having strong regulatory competence in a healthcare, pharmaceutical or MedTech company is critical.

Crossover learning and work-life balance is important for every professional within the healthcare industry – particularly for young and aspiring pharmacists. Be creative, be bold, and utilize your knowledge to do something meaningful for others.

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Pharmacokinetic drug interaction of protein kinase inhibitors

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ABSTRACT

The development of protein kinase inhibitors has revolutionized the management of various types of cancers and other conditions. It has the advantages of oral administration, allowing treatment at outpatient setting thus improves quality of life. Adequate dosing of these group of medications is required to ensure efficacy and avoid toxicity. Protein kinase inhibitors are prone to drug-drug interactions that may affect drug exposure, leading to treatment failure or adverse drug reactions. In particular, pharmacokinetic drug interactions of protein kinase inhibitors is a commonly encountered problem in clinical practice. As the use of multiple concomitant drugs in cancer patient is not uncommon, it is important to identify and manage these drug-drug interactions and to ensure adequate drug exposure. This article will provide an overview of the mechanisms, clinical effects and recommendations on managing various types of pharmacokinetic drug interactions of protein kinase inhibitors. This include (i) interactions with gastric acid suppressants, (ii) interactions with drug transporter system and (iii) interactions with hepatic enzyme systems respectively.

Keywords: *Protein kinase inhibitors, Drug-drug interactions, Pharmacokinetic drug interaction, Gastric acid suppressants, Drug transporter system, Hepatic enzyme systems*

INTRODUCTION

The development of protein kinase inhibitors (PKI) has changed the management of various malignant diseases and conditions. It has improved patient's prognosis and became the standard treatment[1,2] for various types of cancers. Advantages of PKI include oral administration and ease of dosing in outpatient setting which could improve patient's quality of life. Some PKIs have a narrow therapeutic index as there is a strong correlation between the exposure of these drugs and the response or toxicity[1,3]. For instance, pazopanib and sunitinib shows increasing risk of toxicity with plasma concentrations, which could lead to adverse drug effects and necessitate dose reduction. PKI is prone to drug-drug interactions (DDI) which may affect their plasma concentrations and hence the risk of reduced efficacy or increased toxicity. A study shows that the rate of co-prescribing of drugs that interact with PKI in 1-year ranges from 23% to 57%, in which the duration of two treatment overlapping is up to 85% of treatment duration.[4] As the use of multiple medications in cancer patients are common, the presence of clinically-significant drug-drug interactions should be taken as an important consideration during the use of PKI.

PHARMACOKINETIC DRUG INTERACTIONS

Pharmacokinetic drug interactions with PKI could be classified into three categories, and their mechanism of action are discussed below:[1,5,6]

(1) Interaction with gastric acid suppressants

The solubility of some PKI is largely pH-dependent. PKIs are weakly basic and there is an equilibrium between ionized and non-ionized form of the drug. A rise in gastric pH could shift the equilibrium to the non-ionized form, which has lower solubility. Most of the PKIs belong to Class II and Class IV under Biopharmaceutics Classification System,[5] suggesting a low solubility and with different permeability across membranes. Therefore, the absorption, bioavailability and therapeutic effect would decline when PKIs are co-administered with drugs that increases stomach pH value. The presence of achlorhydria (a state in which the production of hydrochloric acid in the stomach is low and the intragastric pH is elevated) in elderly complicates the treatment with PKI.[7]

Proton pump inhibitors, histamine-2 receptor antagonist (H2RA), and antacids are the common groups of drugs that affect PKI absorption in the gastrointestinal tract. Studies show that about 20-30% of cancer patients have an indication for the use of acid suppressive therapy.[8] A study of US populations shows the prevalence of concomitant PKI and PPI was 22.7%,[9] and up to 33% of cancer patients in US are on acid suppressive agents.[10] The most commonly prescribed acid suppressive agents are proton pump inhibitors which accounted for about 65-80% of the cases.[5]

Both US FDA and EMA have provided recommendations on the management of drug-drug interactions between PKI and acid suppressive therapy.[11,12] A summary of pharmacokinetic study results on drug-drug interactions between selected PKI and various acid suppressive therapy is shown on **table 1**. Limitations of these recommendations should be noted, for example few number of patients, short study period, variance in study designs between different drugs. For example, AUC of ceritinib decreased 30% in cancer patients but the effect on steady state exposure is not clinically significant.[13] There were differences in recommendations on management of these interactions between FDA and EMA in some PKIs.[5] Moreover, drug interaction studies were not available in FDA or EMA prescribing information for some of the PKIs. (E.g. Sunitinib)

PKIs that are not expected to be affected by the use of gastric acid suppressants include: Afatinib, Alectinib, Axitinib, Brigatinib,[14] Cabozantinib, Cobimetinib, Crizotinib, Dabrafenib, Entrectinib,[14] Ibrutinib,[1] Imatinib, Lenvatinib , Lorlatinib,[14] Osimertinib, Ponatinib, Regorafenib,[1] Ruxolitinib,[1] Sorafenib,[15] Trametinib,[1] Vandetanib, Vemurafenib.[1]

There are a few long-term data on the effect of these interactions over the efficacy of PKI. For example, a study in Taiwan showed prolonged PPI coverage resulted in a worsening overall survival rate, when comparing with short or no PPI coverage, in patients treated with first line gefitinib for metastatic non-small cell lung cancer (NSCLC).[16] A meta-analysis show that the use of concomitant acid suppressive therapy with PKI associated with a poorer overall survival in patients with NSCLC, but not in patients with renal cell carcinoma.[2] A study reported that plasma concentrations of sunitinib in patients receiving PPI may be suboptimal and may lead to early treatment failure, although sunitinib shows a high gastric solubility.[17]

The general principles for managing drug-drug interactions, concomitant use of PKIs and acid suppressive agent should be reviewed. It is advisable that such combination be avoided, or alternative treatment with less interaction potential be considered a far as possible to reduce the effect on PKI. If the concurrent use is required, the duration of action of acid suppressive therapy must be taken into account. Antacids generally have a short-acting effect on gastric pH. Hence, the effect on PKI's absorption is expected to be smallest when the PKI is administered at least 2 hours before, or 4 hours after taking an antacid.[1,5] H2RA has a duration of action between 10-12 hours. PKIs may be administered 2 hours before, or 10 hours after H2 receptor antagonist, as the pH in this window is expected to be lower. For PPI, the onset of action is usually 3-4 hours after intake. The delayed onset of action is due to the formulation of enteric coated tablet for certain agents (e.g. Pantoprazole), which absorptions occur in the duodenum. Moreover, the inactivation of H+/K+/ATPase in gastric cells takes time. The duration of action of once daily PPI ranges from 12-14 hours[1] and up to 24 hours.[5] If there is a strong indication for PPI, a window of relatively low gastric pH (2 hours before PPI in the morning in a once daily regimen)[1] may be used for administering PKI.

(2) Interactions with drug transporter system

Drug transporters are located throughout the body, especially in the intestines, kidney, bile duct and blood-brain barrier.[1] Drug influx transporter increases the amount of drugs absorbed, while drug efflux transporter

Table 1. Drug-drug interactions between selected protein kinase inhibitors and acid suppressive therapy[11,12,18,19]

PKI	Results from studies	PPIs	H2RA	Antacid
Bosutinib (Bosulif®)	PPI reduces AUC by 26%	Avoid	2 hours before or after H2RA	2 hours before or after antacid
Ceritinib (Zykadia®)	PPI+ Ceritinib for 6 days reduces C_{max} and AUC by 25% and 30%	Use with caution	2 hours before or 10 hours after H2RA	2 hours before or after antacid
Dasatinib (Sprycel®)	PPI reduces AUC by 43%; H2RA reduces AUC by 61%;	Avoid	Avoid	2 hours before or after antacid
Erlotinib (Tarceva®)	PPI reduces AUC by 46%; Once daily H2RA reduces AUC by 33%	Avoid	2 hours before or 10 hours after H2RA	2 hours before or 4 hours after antacid
Gefitinib (Iressa®)	H2RA twice daily reduces AUC by 47%	Avoid, OR 12 hours before or after PPI	6 hours before or after H2RA	6 hours before or after antacid
Lapatinib (Tykerb®)	PPI taken 12 hours before Lapatinib reduceAUC by 26%	Avoid	Avoid	Avoid, OR 1-2 hours before or after antacid[1]
Neratinib (Nerlynx®)	PPI single dose reduces AUC of Neratinib by 70%	Avoid	2 hours before or 10 hours after H2RA	3 hours before or after antacid
Nilotinib (Tasigna®)	PPI reduces AUC by 34%	Avoid	2 hours before or 10 hours after H2RA	2 hours before or after antacid
Pazopanib (Votrient®)	PPI reduces AUC by 40%	Consider antacid, or administer pazopanib without food once daily evening with PPI	Consider antacid, or administer pazopanib 2 hours before or 10 hours after H2RA without food	1 hour before or 2 hours after antacid

Abbreviations: AUC: Area under curve; H2RA: Histamine 2 receptor antagonist; PPI: Proton pump inhibitors; PKI: Protein kinase inhibitors

decreases the amount of drugs absorbed into cells. These drug transporters were also classified into two main groups, namely ATP-binding cassette transporters (ABCs) and the solute carrier transporters (SLCs)[1,14] ABCs are drug efflux transporters. Examples include P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug resistance protein subfamily (MRP) and multi-antimicrobial extrusion protein (MATE). SLCs are drug influx transporter. Examples include organic anion transporting peptides (OATPs), organic anion transporters (OATs), and organic cation transporters (OCTs).

Drug efflux transporter affects enterohepatic recirculation of drugs in the gastrointestinal tract,[1] in which the drug molecules are absorbed through hepatic portal vein, metabolized by hepatic cells and secreted into bile and reabsorbed in the GI tract. Most of the PKIs are substrate of at least one of these drug efflux transporters with a few exceptions[11,12] (e.g. Ibrutinib, Ruxolitinib ,Vandetanib). Most PKIs are itself an inhibitor of these transporter enzymes. The most common transporters involved are P-GP and BCRP.

As a general precaution, it is recommended to avoid the concurrent use of an inducer or inhibitor of the drug transporter if a patient is on a PKI which is a substrate of that transporter, and to avoid the concurrent use of a transporter substrate with narrow therapeutic index when the PKI is an inhibitor of that transporter.[1,5,6,11,12] However, when the concurrent use is required, patients should be monitored for adverse drug reactions as well as the treatment efficacy. Most regulatory agencies recommend against the concurrent use of PKIs with strong P-gp or BCRP inducer and inhibitor and few recommendations on the dosage adjustment and change in administration time is provided[11,12,14] **(Table 2)**. Bosutinib and dabrafenib have minimal clinically significant interactions with drug transporter inhibitor/inducers and the concurrent use is considered safe.

It should be noted that most of these drug interactions studies are in-vitro studies, or prediction was base on physiologically based pharmacokinetic (PBPK) modelling.[1] Nevertheless, some studies were performed in healthy patients but not cancer patients. Cancer patients are more prone to effect of drug interactions due to concomitant medications.

(3) Interaction with hepatic enzymes

Most PKIs are mainly metabolized in liver through phase I metabolism (e.g. CYP system), and a few by phase II metabolism (e.g. UPD-glucuronyltransferases, UGT) to either active or inactive metabolites.[1,5,6] Any drugs that inhibit or induce these enzymes may affect the plasma level of PKIs, and could lead to either toxicity or reduce efficacy. A few PKIs (e.g. Imatinib, pazopanib) are also inhibitors of CYP enzymes that affect exposure of other CYP substrates. Moreover, some CYP enzymes are located in the intestinal wall, which are in close proximity with p-gp transporters. Some PKIs depend on both intestinal and hepatic CYP metabolism and hence it is difficult to determine the main contributor of the reduced bioavailability. Common groups of drugs that cause significant drug interactions include antifungals (e.g. Itraconazole), anti-tuberculosis drugs (e.g. Rifampicin), antibiotics (e.g. Clarithromycin), antiepileptics (e.g. Carbamazepine).[5]

The extent of the interactions can be classified according to the change in exposure (measured by area under curve, AUC) of the PKI from studies. FDA defined that a strong enzyme inhibitor increases the AUC of the interacting drug by more than 5-fold; while a moderate inhibitor and weak inhibitor could increase the AUC by 2 to 5-fold and 1.25 to 2-fold respectively.[5] Similarly, a strong inducer decreases AUC of the interacting drug by more than 80%, while a moderate and weak inducer decrease AUC by 50-80% and 20-50% respectively. The onset of inhibition can be as fast as within 24 hours post-dosing, while the induction of hepatic enzymes (and also drug transporter) take time which usually reaches maximum at 7-10 days.[6]

Table 2 Drug-drug interactions between selected PKIs and drug transporters[11,12,18,19]

Drug Name	Substrate of	Inhibit	Recommendations on change in dosage/administration
Afatinib (Giotrif®)	P-gp, BCRP	P-gp, BCRP	With strong P-gp inhibitors: Reduce dose by 10mg if not tolerated. With strong P-gp inducers: Increase dose of afatinib by 10mg Resume previous dose after discontinuation of P-gp inhibitor/inducer. Administer P-gp inhibitor 6 hours/12 hours apart from afatinib
Cabozantinib (Cabometyx®)	MRP2	P-gp, BCRP, MATE1, MATE2	With strong MRP2 inhibitor: Avoid, or decrease dose by 20 mg With strong MRP2 inducer: Avoid, or increase dose by 20 mg
Ibrutinib (Imbruvica®)	Nil	P-gp, BCRP	Administer P-gp and BCRP substrates 6 hours before or after ibrutinib to minimize interaction
Neratinib (Nerlynx®)	P-gp	P-gp, BCRP	Monitor for patients on P-gp and BCRP substrate carefully Avoid P-gp inducers and inhibitors. Strong P-gp inhibitors: Reduce dose (240mg daily to 40mg daily)
Nintedanib (Ofev®)	P-gp, OCT-1	P-gp, OCT1, BCRP	P-gp inhibitors: reduce to 100mg BD P-gp inducers: consider alternative with no P-gp interaction
Trametinib (Mekinist®)	P-gp	P-gp, BCRP, OAT1/3, OATP1B1/1B3/2B1 OCT2, MATE1	Substrates of drug transporters should be taken 2 hours before or after trametinib.

Abbreviation: BCRP: Breast cancer resistance protein, MATE: multi-antimicrobial extrusion protein; MRP: multidrug resistance protein subfamily; OAT: Organic anion transporters; OATP: Organic anion transporting peptides; OCT: organic cation transporters; P-gp: P-glycoprotein

Table 3. Drug-drug interactions between selected PKIs and hepatic enzymes[11,12,18,19]

PKI	Substrate of	Inhibit	Induce	Specific dosage adjustment recommendations
Axitinib (Inlyta®)	CYP3A4/5(Major) CYP1A2/2C19, UGT1A1 (Minor)	CYP1A2	Nil	Strong 3A4/5 inhibitors: Use half of dose (e.g. start at 2mg BD) and adjust base on individual patient tolerability and safety.
Brigatinib (Alunbrig®)	CYP3A4/5 CYP2C8	Nil	CYP3A4 CYP2C	Strong 3A4 inhibitors: Avoid, or reduce dose by approximately 50% (e.g. 180mg to 90mg, or 90mg to 60mg) Moderate 3A4 inhibitors: Avoid, or reduce dose by approximately 40% (e.g. 180mg to 120mg, 120mg to 90mg, or 90mg to 60mg)
Ceritinib (Zykadia®)	CYP3A4 (Major)	CYP3A4, 2C9, 2A6, 2E1	Nil	Strong 3A4 inhibitors: Avoid use or reduce dose by one-third. Consider increase dose with long term treatment with 3A4 inhibitors.
Dasatinib (Sprycel®)	CYP3A4	CYP3A4, 2C8	Nil	Strong CYP3A4 inhibitors: Avoid, or dose reduction. (140mg to 40mg, 100mg & 70mg to 20mg, 60mg & 40mg to 10mg using solution) Strong CYP3A4 inducers: Avoid use or increase dose with monitoring of toxicity.
Entrectinib (Rozlytrek®)	CYP3A4	CYP3A4	Nil	Strong CYP3A inhibitors: Avoid use, or reduce dose (600mg to 100mg) Moderate CYP3A inhibitors: Avoid use, or reduce dose (600mg to 200mg)
Erlotinib (Tarceva®)	CYP3A4 (Major) CYP1A2/1A1/3B4/ 1B1 (Minor)	CYP1A1, UGT1A1 (potent) CYP2C8, 3A4 (moderate)	Nil	Strong CYP3A4 inhibitors/ combined CYP3A4 and CYP1A2 inhibitor: Avoid, or reduce dose by 50mg decrements Strong CYP3A4 inducers: Avoid, or increase dose by 50mg increments every 2 weeks to maximum 450mg CYP1A2 inducer/smoking: Avoid, or increase dose by 50mg increments every 2 weeks to maximum 300mg
Gefitinib (Iressa®)	CYP3A4 (Major) CYP2D6	CYP2D6	Nil	CYP3A4 inducers: Avoid use or increase dose to 500mg daily.
Ibrutinib (Imbruvica®)	CYP3A4	Nil	Nil	(For B-cell malignancies) CYP3A4 inhibitors (Voriconazole 200mg BD, Posaconazole <200mg BD): 140mg daily CYP3A4 inhibitors (Higher dose posaconazole): 70mg daily Other CYP3A4 inhibitors: Avoid use or withhold up to 7 days. Moderate CYP3A4 inhibitors: Reduce dose to 280mg daily.
Imatinib (Glivec®)	CYP3A4 (Major) CYP2D6,2C9, 2C19 (Minor)	CYP3A4/5, 2C9, 2D6	Nil	Strong CYP3A4 inducers: Avoid use or increase dose by 50% (up to 600mg BD) with monitoring.
Lapatinib (Tykerb®)	CYP3A (Major) CYP2C8,2C19 (Minor)	CYP3A4,2C8	Nil	Strong CYP3A4 inhibitors: Avoid use, or reduce dose to 500mg daily Moderate CYP3A4 inhibitors: Use with caution Strong CYP3A4 inducers: Avoid use, or increase dose gradually (1250mg/1500mg to maximum 4500mg/day or 5500mg/day)
Lorlatinib (Lorbrena®)	CYP3A4 (Major) CYP2C8,2C19,3A5 (Minor)	Nil	CYP3A CYP2B6 CYP2C9	Strong CYP3A4 inhibitors: Avoid use, or reduce starting dose from100mg daily to 75mg daily, or 75mg daily to 50mg daily.
Neratinib (Nerlynx®)	CYP3A4 (Major)	Nil	Nil	Strong CYP3A4 inhibitors: Avoid use, or reduce dose (240mg daily to 40mg daily)
Nilotinib (Tasigna®)	CYP3A4	CYP3A4, 2C8, 2C9, 2D6 UGT1A1	CYP2B6 CYP2C8	Strong CYP3A4 inhibitors: Avoid use, or interrupt, or reduce dose resistant or intolerant Ph+ CML: 400mg BD to 300mg daily; newly diagnosed Ph+ CML-CP: 300mg BD to 200mg daily)
Osimertinib (Tagrisso®)	CYP3A4/3A5	CYP3A4/3A5, UGT1A1	CYP1A2	Strong/moderate CYP3A4 inducers: Avoid use or increase dose to 160mg daily for strong inducers.
Pazopanib (Votrient®)	CYP3A4 (Major) CYP1A2,2C8 (Minor)	CYP3A4, 2B6, 2C8, 2D6, 2E1, UGT1A1	Nil	Strong CYP3A4 inhibitors: Avoid use, or reduce dose (800mg daily to 400mg daily)
Ponatinib (Iclusig®)	CYP3A4 (Major) CYP2C8,2D6 (Minor)	Nil	Nil	Strong CYP3A inhibitors: Reduce starting dose (45mg daily to 30mg daily)
Ruxolitinib (Jakavi®)	CYP3A4 (Major) CYP2C9 (Minor)	Nil	Nil	Strong CYP3A4 inhibitors: Reduce each unit dose by 50% Dual CYP3A4 and 2C9 inhibitor: Reduce each unit dose by 50%
Sunitinib (Sutent®)	CYP3A4	Nil	Nil	Strong CYP3A4 inhibitors: Avoid or reduce dose (37.5mg daily for GIST/MRCC or 25mg for pNET) Strong CYP3A4 inducers: Avoid or increase dose in 12.5mg increment (Max 87.5mg for GIST/MRCC or 62.5mg for pNET)
Vemurafenib (Zelboraf®)	CYP3A4	CYP2C8/9, 1A2	CYP3A4, 2B6	Strong CYP3A4 inducers: Avoid use, or increase dose by 240mg

Abbreviations: BD: Twice daily; CYP: Cytochrome P450; GIST: gastrointestinal stromal tumor; MRCC: Metastatic renal cell carcinoma; pNET: progressive, well-differentiated pancreatic neuroendocrine tumors; Ph+ CML- CP: Philadelphia chromosome–positive chronic myeloid leukemia- Chronic phase; UGT: UPD-glucuronosyltransferases

Interactions of PKI with hepatic enzymes are well-documented in clinical studies and prescribing information. A summary of the interactions, recommended dosage adjustment, and comments on these interactions are provided for selected PKIs in **Table 3**. Most PKIs are metabolized mainly through CYP3A enzymes with a few exceptions[11,12] (e.g. Idelalisib, Lenvatinib, Nintedanib, Trametinib).

The management of this type of drug interaction is to avoid the use of strong enzyme inhibitors or inducers that could interact with the corresponding PKI, and to switch to an alternative agent with less interaction potential. If the concomitant use is strongly indicated, dosage adjustment of the PKI should be considered with careful monitoring of the presence of PKI-specific side effects and the underlying disease control. For most PKIs that are CYP3A substrates, the use of a strong inducer is not recommended as the decrease in drug level cannot be compensated safely by an increase in dosage. Dose reduction of PKI can be adopted with concomitant enzyme inhibitors with careful monitoring of disease control.

It is important to note most dosage adjustment recommendations are based on pharmacokinetic studies, which aim to achieve a similar drug exposure (AUC), but these are not tested in patient populations. It should also be noted that the dose of PKI should be returned to that prior to initiation of CYP inhibitors after the CYP inhibitors are discontinued,[11,12] to reduce the risk of toxicity or lack of efficacy. The time to resume the original dose varies between products.

CONCLUSION

PKIs are important treatment modalities in various types of malignant diseases. However, they have a narrow therapeutic window and are prone to drug-drug interactions. As the use of concomitant drugs with interaction potential is common, drug interactions are of important treatment considerations in clinical use of PKIs. Pharmacokinetic drug-drug interactions of PKI results showed that the concurrent use of gastric acid suppressant agents could affect the absorption, bioavailability and therapeutic effect as most PKI shows pH dependent solubility. The extent of interactions depends on the individual solubility of PKIs and the duration of acid suppression. In addition, interactions with transporter systems (e.g. P-gp) and hepatic enzymes (e.g. CYP3A) greatly affect PKI exposure as most PKIs are substrates of transporter systems, and are metabolized in liver. Some PKIs also inhibits or induces these systems, which could affect the exposure of other drugs. To manage these drug-drug interactions, the indications of the interacting drugs should always be reviewed, and substitution with drugs with less interacting potential should be considered. PKI dosage adjustment or separation of drug administration time could be considered as alternative solutions, but it should be used cautiously due to the lack of in-vivo data to support these recommendations.

Author's background
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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

2 CE Units

Pharmacokinetic drug interaction of protein kinase inhibitors

1. ***Which of the followings are possible mechanisms of pharmacokinetic drug interactions with protein kinase inhibitors?***
   (i) Enhanced absorption due to gastric acid suppressants
   (ii) Interactions with drug transporter at blood brain barrier
   (iii) Reduced clearance through interaction with rifampicin
   A. (i) and (ii)
   B. (ii)
   C. (ii) and (iii)
   D. (i) and (iii)

2. ***Which of the following statement regarding drug interactions between gastric acid suppressants and protein kinase inhibitors is incorrect?***
   A. Always review the indications and the need of gastric acid suppression with proton pump inhibitors.
   B. Antacids have minimal drug interactions with protein kinase inhibitors when administration is separated by 4 hours
   C. Dasatinib can be administered 2 hours before or 10 hours after pantoprazole
   D. Gefitnib can be administered 6 hours before or after famotidine

3. ***Which are the difficulties in the management of drug interactions between protein kinase inhibitors and drug transporter inhibitors/inducers?***
   (i) Protein kinase inhibitors are both substrates and inhibitors of at least one drug transporter system
   (ii) Lack of long-term data on effects of drug interactions in cancer patients
   (iii) Recommendations on dosage adjustment are only based on in-vitro studies
   A. (i) and (ii)
   B. (ii) and (iii)
   C. (i) and (iii)
   D. All of the above

4. ***A strong inhibitor of hepatic enzyme systems increases the drug exposure by:***
   A. 1.25-2 fold
   B. 2-5 fold
   C. > 5-fold
   D. > 10-fold

5. ***Recommendations on dosage adjustment of protein kinase inhibitors with CYP inhibitors aim to achieve a similar ____.***
   A. Tmax
   B. Cmax
   C. AUC
   D. Volume of distribution

6. ***Which of the following protein kinase inhibitors have minimal drug interactions with both gastric acid suppression and drug transporter system?***
   A. Afatinib
   B. Bosutinib
   C. Cabozantinib
   D. Dabrafenib

7. ***Which of the following statement regarding drug interactions between protein kinase inhibitors and hepatic enzyme systems is incorrect?***
   A. Some protein kinase inhibitors are both substrates and inhibitors of CYP450 system
   B. Inhibition of CYP enzymes can be as fast as within 24 hours after first dose
   C. Dose of protein kinase inhibitors should be adjusted to original dose after the interacting drugs is discontinued
   D. Most protein kinase inhibitors metabolized by CYP3A system can be used safely with rifampicin

8. ***Which of the following gastric acid suppression therapy is recommended to a patient on lapatinib?***
   A. Esomeprazole 20mg daily taken 12 hours before lapatinib
   B. Famotidine 20mg daily taken 2 hours before lapatinib
   C. Aluminum hydroxide, Magnesium hydroxide and simethicone taken 2 hours after lapatinib
   D. Magnesium trisilicate taken concomitantly with lapatinib

9. ***Which of the following drug (s) are both substrates and inducers of CYP3A?***
   (i) Osimertinib
   (ii) Gefitinib
   (iii) Lorlatinib
   (iv) Brigatinib
   A. (i) and (ii)
   B. (i) and (iii)
   C. (ii) and (iv)
   D. (iii) and (iv)

10. ***Which of the following should be considered when a patient on ritonavir is prescribed with axitinib?***
    (i) Start at half of the dose and adjust based on tolerability
    (ii) Separate administration by these 2 drugs by at least 4 hours
    (iii) Consider increasing the dose of axitinib from 2mg BD to 5mg BD when ritonavir is discontinued
    A. (i) and (ii)
    B. (ii) and (iii)
    C. (i) and (iii)
    D. All of the above

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 272(D&T)

Pharmacist-led Smoking Cessation: Pharmacological and Non-Pharmacological Options

1. C 2. B 3. B 4. D 5. A 6. B 7. D 8. C 9.C 10. A

Hong Kong women's knowledge, attitude and usage of combined oral contraceptive pills and the role of pharmacist in improving patient care

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ABSTRACT

A total of 357 responses were collected from Hong Kong females aged 18-50 years to describe Hong Kong females' knowledge, attitude and usage of combined oral contraceptive pills (COCP) and to analyze the common misconceptions on COCP usage among Hong Kong females. The mean knowledge score obtained was 17.5±6.32 out of the total score of 39. The mean knowledge scores obtained by current users, past users and non-users of COCP were 19.2±6.3, 17.7±5.9 and 16.9±6.4 respectively. All participants demonstrated knowledge gaps in four knowledge domains. In particular, knowledge deficit is evident for mechanism of action and side effects/drug-interactions of COCP. The internet/ online forum and product information sheet were the preferred information source for drug enquires due to easy accessibility, while healthcare professionals such as pharmacists were the least preferred due to low accessibility. Misconceptions related to knowledge of COCP were identified among respondents of online survey. The low tendency in seeking drug information from healthcare professionals could have potentiated the gap. Further education and enhanced accessibility to pharmacist service in community is warranted to improve general drug literacy.

Keywords: *Combined oral contraceptives, pharmacists, knowledge, attitude, usage, Hong Kong.*

INTRODUCTION

Combined oral contraceptive pill (COCP) is one of the most effective non-invasive contraceptive methods with contraceptive effectiveness at around 91%.[1] Although COCP are available over-the-counter in Hong Kong, prevalence of COCP usage was relatively low at 6.2%, comparing to over 20% in other developed regions, e.g. Northern Europe, Australia and New Zealand in 2019.[2,3,4] The findings from past local studies echoed the United Nations report. One large-scale local study by The Family Planning Association of Hong Kong (HKFPA) reported that among 1295 contraceptive ever-users aged 18 to 45, majority (76.1%) used male condom in past year, followed by coitus interruptus (20.9%) and only 12.6% used COCP.[5]

The underutilization of COCP was widely recognized by local healthcare professionals.[5] Several studies found consistently low knowledge in COCP.[6,7] A local study found that majority of Hong Kong women had misconceptions over the side effect profile of COCP.[7] Majority of the respondents failed to identify correctly the side effects of COCP. It was possible that the misconception about COCP hindered their usage.

Among women who acquired contraceptives, most obtained contraceptive pills from convenience store (52.1%) and dispensary (31.6%).[6] while significant proportion of users obtained contraceptive pills at premises with pharmacists, most women sought information about contraception from health websites (46.5%) and online forums (40.1%).[5] The lack of access to consultation service resulted in fear of side effects.[6] Overseas researchers had established study methodology to evaluate women's knowledge of COCP, and to provide insight into specific areas of contraceptive knowledge that have to be addressed.[8] This study aims to adapt similar methodology in assessing systematically the knowledge gap, attitude and usage of COCP among females in Hong Kong.

AIMS & OBJECTIVES

This study aims to describe Hong Kong females' knowledge, attitude and usage of COCP and to provide insights into enhancement of drug education. This study also aims to identify the association between the knowledge score and females' attitude towards and usage of COCP. Lastly, this study explores the contraceptive behaviors, perception of pharmacist's role in contraceptive counselling and education among Hong Kong females.

METHOD

Study design

An observational cross-sectional survey study was conducted to investigate the knowledge, attitude and usage of COCP among Hong Kong females aged 18-50 using convenience sampling. This study adapts the questionnaire developed for a similar Australian study upon consent granted by the authors.[8] The adapted

instrument consisted of totally 19 questions, including two questions on basic demographic, ten on COCP usage questions, five for knowledge assessment, and two questions on contraception information seeking behavior. Three of the questions constituted a final knowledge assessment score of 39. One score was awarded to each correct answer while no score was given to incorrect response. A score of 80% or above was considered an adequate knowledge level for each individual question.

The survey was translated into Traditional Chinese by the principal investigator, who was a bilingual, user of English and Traditional Chinese. An experienced practicing pharmacist with foreign and local experience was invited to proofread the questionnaire. Pilot evaluation of the instrument was conducted subsequently to validate the questionnaire.

Ethics approval

Ethics approval was obtained from Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) (Ref: UW 19-825).

Subject recruitment & data collection

Hong Kong females aged 18-50 years, regardless of their gynecological disease status and COCP usage history were eligible for the study. The online survey was launched on HKU Qualtrics to collect responses anonymously. Link to the survey was posted online forums with different age group visitors (e.g. Baby Kingdom, StickRiceLove, Little Soldier Forum etc), social media (e.g. Facebook), and via university mass mails from 1st February 2020 to 30th April 2020. Based on the projected total population size of 1,376,420,[9] a minimum of 384 responses is needed to achieve 95% confidence interval with the margin of error at 5%. A total 357 feedbacks were received during the study period.

Statistical Analysis

Data was processed using Microsoft Excel™ and IBM SPSS™ for analysis and computation of total and mean knowledge score. The knowledge score of COCP current-users, past-users and non-users were analyzed and compared using Mann Whitney-U test with a significance level less than or equal to 0.05. The results of demographics and contraceptive information behavior were analyzed descriptively. The survey was attached in Appendix 1.

Data storage and handling

No person identifiable data was collected in this study. All data collected was password-protected and was accessible by the principal investigator only.

RESULTS

Demographics

A total of 357 responses were received during the study period. Basic demographics of the respondents were listed in **Table 1**. Most respondents aged 21-25 years (41.7%) with mean age of 24.8±5.94 years. The highest level of education attained by majority of the respondents was undergraduate degree (45.4%).

Table 1. Basic demographics of the 357 respondents

	N (%)
Q1. Age (years old) (n=357)	
18-20	95 (26.6%)
21-25	149 (41.7%)
26-30	61 (17.1%)
31-35	27 (7.6%)
36-40	16 (4.5%)
40-50	9 (2.5%)
Q2. Education level (n=357)	
Primary or below	0 (0%)
Secondary graduate	82 (23.0%)
Diploma	44 (12.3%)
Undergraduate degree	162 (45.4%)
Postgraduate degree	69 (19.3%)
Others	0 (0%)

COCP usage

Among the 357 respondents, 225 (63.0%) were COCP non-users users, 132 (37.0%) were COCP ever-users, i.e. taken COCP at some point in their lives. Within the group of COCP ever-users, only 60 (45.5%) of them were currently taking COCP and most started COCP within the past one year. Approximately 70% of COCP ever-users took COCP for contraception (66.7%) and dysmenorrhea (28.8%).

While 46% of respondents started to use COCP based on recommendations from non-healthcare professionals, for example family, friends and the internet, most of the COCP ever-users (84.8%) reported that they were informed of the undesirable effects of taking COCP when they first started the therapy. Analysis of usage pattern was conducted in the 132 ever users while knowledge and attitude analysis was performed for the whole sample size. The details of the COCP usage demographics were listed in **Table 2**.

Knowledge domains

1. COCP administration and contraceptive effectiveness

Majority of respondents (95%) answered correctly in the knowledge question that acknowledged the possibility of pregnancy despite perfect use of COCP. There was no difference in performance balanced regardless of their COCP usage history. Meanwhile, only 32% of the participants knew that the active pills could be taken without a pill-free period.

With the pre-established score cutoff at 80% as the adequate knowledge level, only one-fourth of the statements reached the threshold. COCP ever users were not shown to perform significantly better in this knowledge domain.

Table 2. COCP usage information of the 132 COCP ever users	
	N (%) (Total = 132)
Q4. Current COCP usage (n=132)	
Yes	60 (45.5%)
No	72 (54.5%)
Q5. Duration of COCP usage (n=132)	
Less than 1 year	65 (49.2%)
1-5 years	53 (40.2%)
5-10 years	11 (8.33)
More than 10 years	3 (2.3%)
Q6. Had ever missed an active pill (n=132)	
Yes	106 (80.3%)
No	26 (19.6%)
Q7. Frequency of missing an active pill (n=132)	
Never	24 (18.2%)
Only one time	22 (16.7%)
Once a year	19 (14.4%)
Once every few month	52 (39.4%)
Once a month	10 (7.6%)
Once a week	5 (3.8%)
Q8. Annually visiting physician on COCP administration (n=132)	
Yes	61 (46.2%)
No	71 (53.8%)
Q9. Reason for starting COCP (n=132)*	
Dysmenorrhea	38 (28.8%)
Menorrhagia	15 (11.4%)
Ovarian cyst	25 (19.0%)
Endometriosis	6 (4.6%)
Premenstrual emotional disorder (PMS/PMDD)	16 (12.1%)
Contraception	88 (66.7%)
Q10. Who recommended the first COCP usage? (n=132)*	
General practitioner (GP)	36 (27.3%)
Other doctor (e.g. gynecologist)	45 (34.1%)
Family member/s	6 (4.6%)
Family Planning Association of Hong Kong	21 (15.9%)
Nurse (General Practice/Hospital/Clinic)	4 (3.0%)
Pharmacist	4 (3.0%)
Pharmacy shopper (exclude pharmacists)	4 (3.0%)
Friends	29 (22.0%)
The Internet	26 (19.7%)
Others (nurse practitioner)	1 (0.8%)
Q11. Were you informed on the undesirable effect of taking COCP when you first start?	
Yes	112 (84.8%)
No	20 (15.2%)

*the question(s) allow multiple options selection

Regarding factors that affected COCP contraceptive effectiveness, only 2 out of 16 statements achieved the pre-specified 80% passing threshold. Respondents performed the best in understanding that missing an active pill by more than 12 hours and missing 1 or more active pill would reduce the contraceptive effect respectively but only 42% of them were able to spot that missing an active pill by less than 12 hours would not threaten its contraceptive effect. The detailed responses were listed in **Table 3**.

2. COCP mechanism of action

Out of the 357 respondents, only 26 (7.3%) answered the question correctly identified the mechanism of action of COCP. No significant difference of performance was found between COCP ever users and non-users (p=0.94).

3. Risks and benefits of COCP

Respondents were asked to judge if the 15 medical conditions named in question 16 could be positively or negatively affected by usage of COCP. Only about 30% of the respondents correctly identified the two clinical risks that were known to be potentiated by COCP usage. COCP current users generally obtained numerically higher correct rates than the other two sub-groups in this knowledge domain.

Question 17 was a question investigating respondents' understanding on factors that would potentiate the risk of developing thromboembolism. All 3 options provided were the known risk factors, namely aged above 35 years old, obesity and smoking. 16 (26.7%) current users, 20 (27.8%) past users and 61 (27.1%) non-users answered this question perfectly, without a significant difference between the groups.

Total knowledge scores

The mean total knowledge score for all respondents was 17.5±6.32 out of the maximum total of 39. Among the 357 participants, only 58 obtained 50% of the maximum possible knowledge score. COCP current users obtained a mean total knowledge score of 19.2±6.3. Past COCP users obtained a mean total knowledge score of 17.7±5.9. The lowest mean knowledge score of 16.9±6.4 was found in the COCP non-user group. COC current users scored significantly higher score than non-users (p=0.005) and COC past users (p=0.04).

Contraception information sources

Information source for COCP administration

Majority of the 357 respondents reported that the internet or online forum were their major source of information (77.9%). Product information sheet was the second major source (63.8%). Interestingly, healthcare professionals were not considered major source of information.

The reason for choosing or not choosing the particular source of information was further explored in the questionnaire. Accessibility was the major reason of choosing the internet or online forum. Over half of the respondents reflected that accessibility was also the major reason for not choosing pharmacist and nurse. Other reasons of not choosing pharmacists as primary source of drug information include "pharmacist in the UK provide consultations and prescriptions but pharmacist in HK is a little different to say" and "pharmacists in the drug store are not professional and those pharmacists in the clinic are not accessible". Details of the responses in this question were outlined in **Table 5**.

Table 3. Participants responses to general knowledge questions related to COCP administration and factors affecting its contraceptive effects

	Yes (%)	No (%)	Don't know (%)	Number of current COCP users correct (n=60)	Number of previous COCP users correct (n=72)	Number of non-COCP ever users correct (n=225)
Q13. General COCP administration knowledge (* indicates the correct answer)						
The pill needs to be taken every day to be an effective contraceptive	**288 (80.7%)***	48 (13.5%)	21 (5.9%)	56 (93.3%)	65 (90.3%) (p=0.78)	167 (74.2%) (p=0.02)
The pill should be taken at approximately the same time every day	**263 (73.7%)***	59 (16.5%)	35 (9.8%)	59 (98.3%)	60 (83.3%) (p=0.14)	144 (64.0%) (p<0.00001)
It is acceptable to continue taking active tablets without taking the inactive tablets in between	**114 (31.9%)***	92 (25.8%)	151 (42.3%)	23 (38.3%)	32 (44.4%) (p=0.22)	59 (26.2%) (p=0.55)
The pill is the most effective form of contraception currently available when used correctly	158 (44.3%)	**160 (44.8%)***	39 (10.9%)	12 (20.0%)	32 (44.4%) (p=0.01)	116 (51.6%) (p<0.00001)
It is possible to fall pregnant while taking the pill even with perfect use	**338 (94.7%)***	12 (3.4%)	7 (2.0%)	58 (96.7%)	68 (94.4%) (p=0.83)	212 (94.2%) (p=0.77)
It is important to take a break from using the pill	94 (26.3%)	**143 (40.1%)***	120 (33.6%)	23 (38.3%)	26 (36.1%) (p=0.29)	94 (17.8%) (p=0.73)
COCP could also be used to treat certain gynecological diseases, e.g. ovarian cysts, endometriosis	**257 (72.0%)***	34 (9.5%)	66 (18.5%)	45 (75.0%)	56 (77.8%) (p=0.79)	156 (69.3%) (p=0.51)
Switching between COCP will reduce the effectiveness of contraceptives	20 (5.6%)	**151 (42.3%)***	186 (52.1%)	19 (31.7%)	24 (33.3%) (p=0.21)	108 (48.0%) (p=0.04)
Q15. Factors that could potentially reduce the contraceptive effect of COCP (* indicates the correct answer)						
Missing one active pill by less than 12 hours	114 (31.9%)	**151 (42.3%)***	92 (25.8%)	31 (51.7%)	32 (44.4%) (p=0.05)	88 (39.1%) (p=0.60)
Missing one active pill by more than 12 hours	**301 (84.3%)***	6 (1.7%)	50 (14.0%)	55 (91.7%)	65 (90.3%) (p=0.86)	181 (80.4%) (p=0.14)
Missing more than one active pill	**295 (82.6%)***	21 (5.9%)	41 (11.5%)	54 (90.0%)	60 (83.3%) (p=0.60)	181 (80.4%) (p=0.28)
Missing one or more inactive pill/s	133 (37.3%)	**124 (37.3%)***	100 (28.0%)	17 (28.3%)	26 (36.1%) (p=0.30)	81 (36.0%) (p=0.18)
St John's Wort herbal preparation	**56 (15.7%)***	20 (5.60%)	281 (78.7%)	4 (6.7%)	8 (11.1%) (p=0.98)	44 (19.6%) (p=0.11)
Epilepsy medications such as phenytoin or carbamazepine	**66 (18.5%)***	20 (5.6%)	271 (75.9%)	13 (21.7%)	15 (20.8%) (p=0.95)	38 (16.9%) (p=0.27)
Vomiting	**183 (51.3%)***	53 (14.9%)	121 (33.9%)	31 (51.7%)	47 (65.3%) (p=0.24)	105 (46.7%) (p=0.39)
Severe diarrhoea	**140 (39.2%)***	70 (19.6%)	147 (41.2%)	19 (31.7%)	39 (54.2%) (p=0.01)	82 (36.4%) (p=0.11)
Smoking	80 (22.4%)	**114 (31.9%)***	163 (45.7%)	17 (28.3%)	22 (30.6%) (p=0.06)	75 (33.3%) (p=0.01)
Antibiotics such as Rifampicin and Rifabutin	**98 (27.5%)***	42 (11.8%)	217 (60.8%)	14 (23.3%)	17 (23.6%) (p=0.52)	68 (30.2%) (p=0.23)
Other antibiotics *(When taken without side-effects like vomiting/diarrhoea)*	53 (14.9%)	**89 (24.9%)***	215 (60.2%)	13 (21.7%)	11 (15.3%) (0.54)	65 (28.9%) (p=0.03)
Cimetidine (a gastric acid suppressant)	**66 (19.5%)***	61 (17.1%)	230 (64.4%)	3 (5.0%)	15 (20.8%) (p=0.70)	48 (21.3%) (p=0.40)
Common cold-and-flu med such as paracetamol and chlorpheniramine	20 (5.6%)	**180 (50.4%)***	157 (44.0%)	37 (61.7%)	38 (52.8%) (p=0.99)	105 (46.7%) (p=0.67)
Multi-vitamins	8 (2.2%)	**255 (71.4%)***	84 (26.3%)	52 (86.7%)	50 (69.4%) p=0.67)	153 (68.0%) (p=0.05)
Minor alcohol consumption *(e.g. an occasional alcoholic drink/s not on a regular basis)*	49 (13.7%)	**200 (56.0%)***	108 (30.3%)	46 (76.7%)	36 (50.0%) (p=0.98)	118 (52.4%) (p=0.42)
Excessive alcohol consumption *(e.g. drinking amounts that cause vomiting, diarrhoea, poor concentration or memory, or significant liver damage)*	**230 (64.4%)***	27 (7.6%)	100 (28.0%)	40 (66.7%)	48 (66.7%) (p=0.87)	142 (63.1%) (p=0.43)

Table 4. Participants responses to general knowledge questions related to level of risks for various conditions affected by COCP

	Increase (%)	Decreases (%)	No effect (%)	Don't know (%)	Number of current COCP users correct (n=60) (%)	Number of previous COCP users correct (n=72) (%)	Number of non-COCP ever users correct (n=225) (%)
Q16. Please indicate whether you think taking the pill decreases, has no effect, or increases the risk/s of the following?							
Ectopic pregnancy	55 (15.4%)	**66 (18.5%)***	144 (40.3%)	92 (25.7%)	17 (28.3%)	13 (18.1%) (p=0.61)	36 (16.0%) (p=0.02)
Birth defects	52 (14.6%)	9 (2.52%)	**227 (63.6%)***	69 (19.3%)	43 (71.7%)	34 (47.2%) (p=0.03)	150 (66.7%) (p=0.34)
Infertility	100 (28.7%)	7 (2.00%)	**207 (58.0%)***	43 (12.0%)	46 (76.7%)	37 (51.4%) (p=0.19)	131 (58.2%) (p=0.08)
Cardiovascular disease *(e.g. stroke, blood clots, high blood pressure)*	**139 (29.4%)***	16 (4.5%)	116 (32.5%)	86 (24.1%)	32 (53.3%)	37 (51.7%) (p=0.83)	70 (31.1%) (p=0.005)
Benign (non-cancerous) breast disease	106 (29.7%)	**48 (13.5%)***	70 (19.6%)	133 (37.3%)	5 (8.3%)	9 (12.5%) (p=0.005)	34 (15.1%) (p=0.25)
Functional ovarian cysts	83 (23.3%)	**132 (37.0%)***	47 (13.2%)	95 (26.6%)	26 (43.3%)	21 (29.2%) (p=0.50)	85 (37.7%) (p=0.04)
Endometriosis associated pain	61 (17.1%)	**153 (42.9%)***	26 (7.3%)	117 (32.8%)	31 (51.7%)	24 (33.3%) (p=0.05)	98 (43.6%) (p=0.03)
Breast cancer	**112 (31.4%)***	24 (6.7%)	91 (25.5%)	130 (36.4%)	21 (35.0%)	24 (33.3%) (p=0.10)	67 (29.8%) (p=0.35)
Ovarian cancer	86 (24.1%)	**77 (21.6%)***	54 (15.1%)	140 (39.2%)	13 (21.7%)	15 (20.8%) (p=0.12)	49 (21.8%) (p=0.89)
Endometrial cancer	70 (19.6%)	**85 (23.8%)***	48 (13.5%)	154 (43.1%)	23 (38.3%)	21 (29.2%) (p=0.10)	41 (18.2%) (p=0.05)
Menstrual problems *(e.g. irregular or painful periods, excessive bleeding)*	70 (19.6%)	**238 (66.7%)***	27 (7.6%)	22 (6.2%)	48 (80.0%)	47 (65.3%) (p=0.03)	143 (63.6%) (p=0.72)
Acne	114 (31.9%)	**167 (46.8%)***	23 (6.4%)	53 (14.9%)	44 (73.3%)	41 (56.9%) (p=0.60)	82 (36.4%) (p=0.44)
Weight gain	230 (64.4%)	10 (2.8%)	**40 (11.2%)***	77 (21.6%)	12 (20.0%)	6 (8.3%) (p=0.005)	22 (9.8%) (p=0.49)
Pelvic inflammatory disease	48 (13.5%)	**26 (7.3%)***	107 (30.0%)	176 (49.3%)	6 (10.0%)	13 (18.1%) (p=0.01)	7 (3.1%) (p=0.49)
Contracting sexually transmitted infections (STIs) and/or HIV	31 (8.7%)	35 (9.8%)	**255 (71.4%)***	34 (9.5%)	44 (73.3%)	40 (55.6%) (p=0.01)	171 (76.0%) (p=0.03)

Table 5. Information source for COCP administration

Where do you get your information regard administration of the pill?			Can you successfully find the satisfactory info from the source you chose?	
	Yes (%)	No (%)	Yes (%)	No (%)
General Practitioner	143 (40.2%)	214 (59.8%)	193 (54.1%)	164 (45.9%)
Friends/Family member/s	129 (36.1%)	228 (63.9%)	108 (30.3%)	249 (69.7%)
Other doctor (e.g. Gynaecologist)	149 (41.8%)	208 (58.2%)	187 (52.5%)	170 (47.5%)
The Internet/Online forum	278 (77.9%)	79 (22.1%)	193 (54.1%)	164 (45.9%)
Pharma industry enquiry hotline	9 (2.5%)	348 (97.5%)	67 (18.9%)	290 (81.1%)
Product information sheet (included in pill box)	228 (63.8%)	129 (36.1%)	219 (61.5%)	138 (38.5%)
Pharmacist	64 (18.0%)	293 (82.0%)	102 (28.7%)	255 (71.3%)
Nurse	67 (18.9%)	290 (81.1%)	105 (29.5%)	252 (70.5%)
Others	26 (7.4%)	331 (92.6%)	61 (17.2%)	296 (82.8%)

Information source for COCP adverse events/drug interactions

Similar to the case of information of COCP administration, the internet (66.4%) and product information sheet (54.6%) were the two most popular information origins. However, Over 50% of the respondents claimed they were unable to obtain information to address their concern. Accessibility became the major reason of referring to online information sources and not referring to healthcare professionals such as pharmacists and nurses. Details of the responses in this question were outlined in **Table 6**.

DISCUSSION

Contraception usage habit in Hong Kong

Among the 357 responses, only 37% of them were

COCP ever users. Among them, only 67% started COCP for contraception purposes while the others were taking COCP for gynecological diseases. The estimated prevalence of COCP usage for contraception in Hong Kong was 24.8%. Comparing with the United Nations *Contraceptive Use by Method 2019: Data Booklet*, the prevalence of contraceptive pill usage in Hong Kong was estimated to be 6.2%.[4] Our research found a 4-fold higher COCP usage, which was close to the usage pattern in other developed regions.[4]

Apart from COCP usage, the most common contraceptive method used among the 357 respondents was male condom (59.4%), followed by safe period (22.7%) and coitus interruptus (17.6%). These findings were generally higher than the previously reported prevalence of male condom, rhythm and withdrawal usage at 32.1%, 2.4% and 2.5% respectively. The differences could be contributed by different data collection and analysis model, different sample size and different years of data collection. Nevertheless, the findings in this study enrich our understanding of the contraception usage in Hong Kong.

COCP usage pattern in ever users

COCP requires daily administration to keep the contraceptive efficacy. Although some of the COCP provides a 12-hour or even 24-hour miss dose window, the complexity in administration could possibly cause unintentional non-compliance in COCP users.[10,11] In this study, only 18.2% of COCP users had never missed an active pill. Majority of the users had missed an active pill once every few months (39.4%). The missed pill pattern observed in the study population echoed the findings in a similar Australian study, in which 80% of respondents had missed an active pill and majority missed an active tablet once every few months (38%).[8]

COCP were classified as non-poison by law in Hong Kong and are available over-the-counter without consulting physicians or pharmacists. In this study, majority of the COCP users (61.4%) first started the treatment under recommendation by physicians (general practitioner and other specialists, e.g. gynecologists). Among all healthcare professionals options, pharmacist was the least chosen option chosen. Only 3% of the COCP ever users started COCP with pharmacists' advice. Besides healthcare professionals, friends (22.0%) and the Internet (19.7%) were shown to have high influence on COCP first usage.

Most users of COCP believed they were informed on the undesirable effect of COCP. However, the knowledge score of the respondents was below the margin of passing, most noticeably in the aspect of side effect profile of COCP.

Knowledge score

The respondents of this study obtained a mean knowledge score of 17.5 out of 39. This unsatisfactory COCP knowledge is echoed by another local study, where the subjects also obtained a mean COCP knowledge score of 5 out of 22. In this study, current users of COCP demonstrated significantly better performance than past users and non-users. The result was understandable as COCP current users shall generally be more concerned about the administration, risk and benefits associated with COCP.

Generally, respondents demonstrated relatively better understanding in administration and contraceptive effectiveness. Respondents performed less well in knowledge assessment related to mechanism of action and risks and benefits of COCP.

With respect to the administration of COCP, respondents demonstrated poor knowledge in complex administration and handling of the pill-free or inactive pill period. Poor knowledge of COCP administration is an alarming sign as pill failure and unwanted pregnancy could result.[12] Similar to overseas study, users of COCP in this study could not well identify the risk and benefits associate with COCP use.[8] While 71% of respondents correctly pointed out risk of contracting sexually transmitted infections despite the use of COCP, only 11.2% correctly identified the neutral impact of COCP administration on body weight. This finding corresponds to another local study where only 10.3% of the participants answered the same question correctly.[7] This mismatch in COCP side effects belief and fact was a possible factor contributing to the much lower COCP usage compared with other developed countries.[4] In the same local study, the top 3 reasons for Hong Kong mothers disagreeing the use of COCP by their daughters for menstrual problems

Table 6. Information source for COCP adverse events/drug interactions

Where do you get your information if you experience adverse events/drug interaction?			Can you successfully find the satisfactory info from the source you chose?	
	Yes (%)	No (%)	Yes (%)	No (%)
General Practitioner	150 (42.0%)	207 (58.0%)	186 (52.1%)	171 (47.9%)
Friends/Family member/s	81 (22.7%)	276 (77.3%)	81 (22.7%)	276 (77.3%)
Other doctor (e.g. Gynaecologist)	147 (41.2%)	210 (58.8%)	180 (50.4%)	177 (49.6%)
The Internet/Online forum	237 (66.4%)	120 (33.6%)	168 (47.1%)	189 (52.9%)
Pharma industry enquiry hotline	12 (3.4%)	345 (96.6%)	66 (18.5%)	291 (81.5%)
Product information sheet (included in pill box)	195 (54.6%)	162 (45.4%)	189 (52.9%)	168 (47.1%)
Pharmacist	60 (16.8%)	297 (83.2%)	117 (32.8%)	240 (67.2%)
Nurse	72 (20.2%)	285 (79.8%)	105 (29.4%)	252 (70.6%)
Others	21 (5.9%)	336 (94.1%)	45 (12.6%)	312 (87.4%)

were: poor knowledge on COCP (48.0%), worry about side effects of weight gain and water retention (45.0%) and worry about long-term side effects like infertility, carcinogenicity, and teratogenicity (37.7%).[7] Another local study by HKFPA also found that fear of side effects (e.g. weight gain, irregular bleeding) was the major reason of not using COCP for contraception.[7] Nevertheless, result from this study proved that the side effects deterring the start of COCP in the local population due to misconceptions of risks associated with COCP.

Thromboembolism was a boxed warning and well-known serious side effect of COCP.[11] According to the warning, smoker women over 35 years old shall not start COCP. It was important for the users to identify the risk factors which could potentiate this serious adverse event. Disappointingly, only 27.2% respondents answered this question correctly. Given the over-the-counter legal classification of COCP, the risk posed on the COCP users would be higher than that in other countries where COCP was prescribed or supplied by healthcare professionals, e.g. pharmacists and doctors.

Source of Information

With poor knowledge reflected in this study and with 39.4% COCP ever-users missing active pills once every few months, one would expect users of COCP to seek information administration. Most of the respondents preferred seeking help online (77.9%) or via product information sheet (63.8%) due to better accessibility. Unexpectedly, privacy was not the major reason of opting for these sources. While users preferred to acquire the contraceptives at chain healthcare store, convenience store and pharmacy/dispensary,[6,5] pharmacist was the least preferred source of information with regards to COCP administration due to low accessibility. Individual respondents also suggested that Hong Kong pharmacists were not as professional as foreign pharmacists. Similar findings were observed with regards to the information of COCP side effects and drug-drug interactions.

Implication for clinical practice and education

Although COCP is a non-invasive option with higher contraceptive efficacy, the usage of COCP in Hong Kong was lower than other developed regions.[1,5] Results from this study demonstrated a clear gap between respondents' believes and facts about COCP administration methods, side effects, drug-drug interaction, mechanism of action and risk factors causing thromboembolism in women. Past local studies found that majority of Hong Kong women were reluctant to start COCP because of misconceptions and fear of side effects.

While most of the COCP users purchased contraceptives from chain healthcare stores, convenience store and pharmacy/dispensary, pharmacist was the least preferred healthcare professional to consult when they have drug-related enquiry. Pharmacists are primary healthcare provider who receive specialized training in drug-related issues and provide free-of-charge services in the community. In view of the identified misconceptions and knowledge deficit in COCPs among local users, and pharmacies as popular source of COCP supply, pharmacists could play a key role to offer professional consultations on COCP use. To improve accessibility to pharmacist service, pharmacies can make clear distinction and identification of pharmacist in a store, and provide of drug counselling service only via pharmacists.

Limitations

The online data collection in this study might have jeopardized the enrollment of tech-naïve groups. As a result, the participants were generally younger ones in the target population. This limitation was addressed by distributing the survey to different forums that covered different age-groups and seeking assistance from users' family members. As a result, different age-groups were recruited in this study. Due to feasibility issue, the study was conducted with convenient sampling.

Since the survey was named explicitly as a study related to COCP, non-COCP users might be relatively less engaged to participate in the survey as they might not consider this topic as relevant to them. It might be a possible explanation on the higher than expected proportion of COCP users than the ratio found by United Nations.

Due to the short data collection period, the total number of responses collected was fewer than pre-specified sample size. However, given the results were consistent with other local studies and foreign study findings and the confidence interval incurred from 357 samples was 5.19, the impact from smaller sample size on results interpretation was believed to be minimal.

CONCLUSION

Hong Kong women aged 18-50 years old demonstrated a substantial knowledge deficit in different aspects of COCP despite majority believed they were sufficiently educated on side effects when first started the treatment. The misconceptions of COCP also extended to the side effect profile of COCP, which constituted the major resistance to start treatment. Easily accessible online platforms were the preferred source of information about COCP administration and side effects or drug interactions. Healthcare professionals were not the preferred primary source of information due to low accessibility as perceived by respondents. Role of pharmacists can be further strengthened in the community to address the gap in accessible COCP counselling services.

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Appendix 1. Survey

This survey should take no longer than 15 minutes to complete and all information is anonymous. You are free to choose not to participate at any time while completing this survey. You can choose not to answer questions if you wish. As this survey is anonymous, researchers will not be able to identify your information and therefore your survey will not be able to be withdrawn once submitted.

Please be advised that the Combined Oral Contraceptive Pill (COCP) will be referred to as 'the pill' for the purpose of this survey. Additionally, 'active' tablets refer to those which contain hormones. 'Inactive' tablets contain no hormones and are commonly referred to as "sugar pills".

Survey Questions

Indicate your response by placing a tick or cross in the appropriate box.

1. **Your Age:**
   18-20 ☐ 21-25 ☐ 26-30 ☐ 31-35 ☐ 36-40 ☐ 40-50 ☐

2. **Highest level of education completed:**
   ☐ Primary or below ☐ Secondary graduate
   ☐ Diploma ☐ Undergraduate degree
   ☐ Postgraduate degree ☐ Other …….....

3. **Have you ever taken the pill?**
   Yes ☐ No ☐ If No, please skip to Q.12

4. **Are you currently taking the pill?** Yes ☐ No ☐

5. **For what period of time were you/have you been taking the pill?**
   Less than 1 year ☐ 1-5 years ☐
   5-10 years ☐ More than 10 years ☐

6. **Have you/did you ever miss taking an active tablet?**
   Yes ☐ No ☐ Don't Know ☐

7. **On average, how frequently would you/did you miss taking an active tablet?**
   ☐ Never ☐ Once a week
   ☐ Once every few months ☐ Only one time
   ☐ Once a month ☐ Once a year

8. **Do you consult physician yearly on your COPC administration?**
   Yes ☐ No ☐

9. **What is the reason for using COPC?**
   ☐ Dysmenorrhea ☐ Menorrhagia
   ☐ Ovarian cyst ☐ Endometriosis
   ☐ Premenstrual emotional disorder (PMS/PMDD)
   ☐ Contraception

10. **Who recommended you to start COPC?**
    ☐ General Practitioner (GP) ☐ Friends
    ☐ Other doctor (e.g. Gynaecologist) ☐ The Internet
    ☐ Family member/s ☐ Pharmacist
    ☐ Family Planning Association of Hong Kong
    ☐ Pharmacy shopper (exclude pharmacist)
    ☐ Nurse (General Practice/Hospital/Clinic)
    ☐ Other ……

11. **Are you informed on the undesirable effects of taking COPC when you first start?**
    Yes ☐ No ☐

12. **Other contraceptive method(s) you used in past 1 year?**
    ☐ Male condom ☐ Female condom
    ☐ Progestin-only pill ☐ Contraceptive injection
    ☐ Coitus interruptus ☐ Intrauterine device (IUD)
    ☐ Safe period ☐ Other……..

13. **Please select 'Yes', 'No' or 'Don't Know' to best answer the following statements.**

    a) The pill needs to be taken every day to be an effective contraceptive
    Yes ☒ No ☐ Don't Know ☐

    b) The pill should be taken at approximately the same time every day
    Yes ☒ No ☐ Don't Know ☐

    c) It is acceptable to continue taking active tablets without taking the inactive tablets in between
    Yes ☒ No ☐ Don't Know ☐

    d) The pill is the most effective form of contraception currently available when used correctly
    Yes ☐ No ☒ Don't Know ☐

    e) It is possible to fall pregnant while taking the pill even with perfect use
    Yes ☒ No ☐ Don't Know ☐

    f) It is important to take a break from using the pill
    Yes ☐ No ☒ Don't Know ☐

    g) COPC could also be used to treat certain gynaecological diseases, e.g. ovarian cysts, endometriosi
    Yes ☒ No ☐ Don't Know ☐

    h) Switching between COC will reduce the effectiveness of contraceptives
    Yes ☐ No ☒ Don't Know ☐

** One point awarded to each correct response (indicated by a cross) and zero points for incorrect responses for a total score out of 8.*

14. The pill uses manufactured hormones that act like normal female hormones and prevent pregnancy by (select all answers that may apply):

Killing sperm that enter the woman's body ☐

Thickening mucus released from the cervix ☒

Preventing the release of the egg (ovulation) in women ☒

Making it harder for a developing embryo to lodge in the wall of the womb (endometrium) ☒

Making it harder for the sperm to combine with the egg ☐

(Correct response indicated by a cross)

15. Which of the following could potentially reduce the contraceptive effect of the pill?

Missing one active pill by less than 12 hours
Yes ☐ No ☒ Don't Know ☐

Missing one active pill by more than 12 hours
Yes ☒ No ☐ Don't Know ☐

Missing more than one active pill
Yes ☒ No ☐ Don't Know ☐

Missing one or more inactive pill/s
Yes ☐ No ☒ Don't Know ☐

St John's Wort herbal preparation
Yes ☒ No ☐ Don't Know ☐

Epilepsy medications such as phenytoin or carbamazepine
Yes ☒ No ☐ Don't Know ☐

Vomiting Yes ☒ No ☐ Don't Know ☐

Severe diarrhoea Yes ☒ No ☐ Don't Know ☐

Smoking Yes ☐ No ☒ Don't Know ☐

Antibiotics such as Rifampicin and Rifabutin
Yes ☒ No ☐ Don't Know ☐

Other antibiotics
(When taken without side-effects like vomiting/diarrhoea)
Yes ☐ No ☒ Don't Know ☐

Cimetidine (a gastric acid suppressant)
Yes ☒ No ☐ Don't Know ☐

Common cold-and-flu med such as paracetamol and chlorpheniramine
Yes ☐ No ☒ Don't Know ☐

Multi-vitamins Yes ☐ No ☒ Don't Know ☐

Minor alcohol consumption
(E.g. an occasional alcoholic drink/s not on a regular basis)
Yes ☐ No ☒ Don't Know ☐

Excessive alcohol consumption
(E.g. drinking amounts that cause vomiting, diarrhoea, poor concentration or memory, or significant liver damage)
Yes ☒ No ☐ Don't Know ☐

** One point awarded to each correct response (indicated by a cross) and zero points for incorrect responses for a total score out of 16.*

16. Please indicate whether you think taking the pill decreases, has no effect, or increases the risk/s of the following:

Ectopic pregnancy Decreases ☒ No Effect ☐ Increases ☐ Don't Know ☐

Birth defects Decreases ☐ No Effect ☒ Increases ☐ Don't Know ☐

Infertility Decreases ☐ No Effect ☒ Increases ☐ Don't Know ☐

Cardiovascular disease:
(E.g. Stroke, blood clots, high blood pressure)
Decreases ☐ No Effect ☐ Increases ☒ Don't Know ☐

Benign (non-cancerous) breast disease
Decreases ☒ No Effect ☐ Increases ☐ Don't Know ☐

Functional ovarian cysts
Decreases ☒ No Effect ☐ Increases ☐ Don't Know ☐

Endometriosis associated pain
Decreases ☒ No Effect ☐ Increases ☐ Don't Know ☐

Breast cancer Decreases ☐ No Effect ☐ Increases ☒ Don't Know ☐

Ovarian cancer Decreases ☒ No Effect ☐ Increases ☐ Don't Know ☐

Endometrial cancer Decreases ☒ No Effect ☐ Increases ☐ Don't Know ☐

Menstrual problems:
(Irregular or painful periods, excessive bleeding)
Decreases ☒ No Effect ☐ Increases ☐ Don't Know ☐

Acne Decreases ☒ No Effect ☐ Increases ☐ Don't Know ☐

Weight gain Decreases ☐ No Effect ☒ Increases ☐ Don't Know ☐

Pelvic inflammatory disease

Decreases ☒ No Effect ☐
Increases ☐ Don't Know ☐

Contracting sexually transmitted infections (STIs) and/or HIV

Decreases ☐ No Effect ☒
Increases ☐ Don't Know ☐

** One point awarded to each correct response (indicated by a cross) and zero points for incorrect responses for a total score out of 15.*

17. Which of the following can potentially increase a woman's risk of developing blood clots while taking the pill? Select all answers that may apply.

Age over 35 years ☒ Obesity ☒ Smoking ☒

(Correct response indicated by a cross)

18. Where do you get your information regarding administration of the pill? Select all answers that apply to you.

☐ General Practitioner (GP)
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ Friends/ Family member/s
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ Other doctor (e.g. Gynaecologist)
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ The Internet/ Online forum
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ Pharma industry enquiry hotline
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ Product Information Sheet (Included in pill box)
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ Pharmacist
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ Nurse (General Practice/Hospital/Clinic)
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ Other ……
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

19. Where do you get your information if you experience adverse events/drug interaction? Select all answers that apply to you.

☐ General Practitioner (GP)
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ Friends/ Family member/s
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ Other doctor (e.g. Gynaecologist)
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ The Internet/ Online forum
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ Pharma industry enquiry hotline
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ Product Information Sheet (Included in pill box)
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisf actory info from the source you chose?
☐ Yes ☐ No

☐ Pharmacist
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ Nurse (General Practice/Hospital/Clinic)
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

☐ Other ……
Why or why not?
☐ Privacy ☐ Accessibility
☐ Professionalism ☐ Price
☐ Others

Can you successfully find the satisfactory info from the source you chose?
☐ Yes ☐ No

Thank you for your participation.

* Correct responses and the subsequent mark for questions 13, 15 and 16 were combined for a total mark out of 39. This data was utilised to create the 'total knowledge score' for each participant.

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SUCRATE® gel

(Sucralfate 1g/5ml)

Actively treat GERD & Gastritis with lesser early relapse
Heal damaged G.I. lesions & promote complete recovery

Indication
Gastro-esophageal reflux disease (GERD), gastritis and peptic ulcers of various origin

Composition
Per 5ml sachet containing 1 gram of sucralfate gel

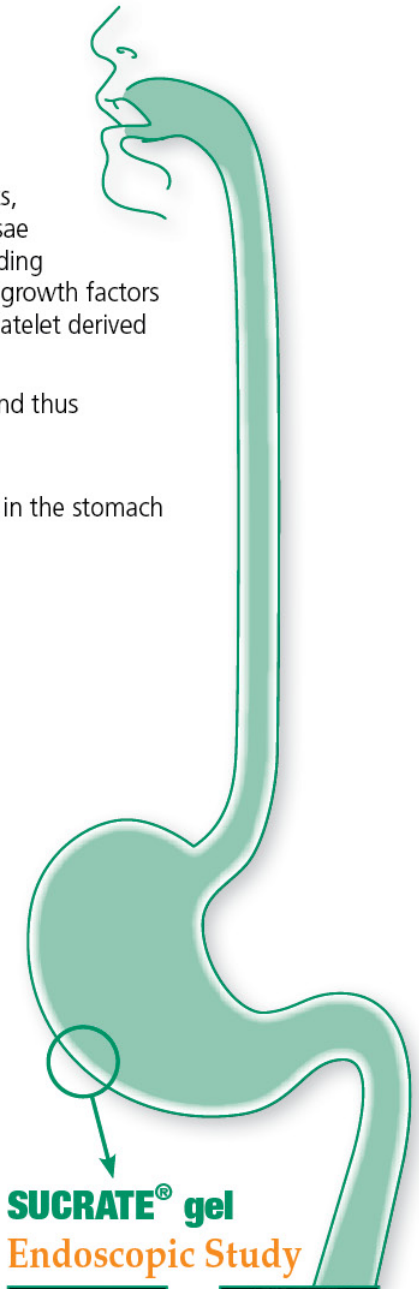
Product mechanism and features
Not offered by any Proton Pump Inhibitors, H2-blockers or other acid suppressing agents, Sucrate Gel uniquely forms a cyto-protective layer on the inflamed and damaged mucosae of the G.I. tract. This layer prevents stomach acid, pepsin and bile salts from further eroding the ulcerated tissues. Also, Sucrate Gel stimulates the production of endogenous tissue growth factors (epidermal growth factor, fibroblast growth factor, transforming growth factor alpha, platelet derived growth factor), which promote cell regeneration and angiogenesis.

Active ulcer healing is achieved through better reconstruction of mucosal architecture and thus prevents early relapse.

- Patented gel form with double surface area of bio-adhesion to ulcerated G.I. tissues
- Does not affect acid secretion - no influence on digestion and micro-organism killing in the stomach (especially relevant for the weak elderly)
- Easily swallowed with good tolerance

Dosage
One sachet 2-4 times a day, according to physician's judgement.

Manufacturer & origin
Product of Lisapharma S.p.A., Italy.
Made in Italy.



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Distributor:

Mekim 美儉有限公司

Product Enquiry: 2774 8385

SHPHK – The New Normal

2020 has been an uneasy year to every one of us. The sudden outbreak of COVID-19 affects the way we live, work and interact with others. We have to adjust ourselves to this 'new normal' and maintain a positive state of mind to get through the COVID crisis.

Regardless of the fierce epidemic, the Society of Hospital Pharmacists of Hong Kong (SHPHK) would continue to organise different educational activities to help its members to maintain their continuing professional development, and to explore new opportunities for professional growth and development.

Hong Kong Pharmacist Vaccinators' Training Pathway and Programme

In September, the Hong Kong Society for Travel Medicine, Department of Pharmacology and Pharmacy, The University of Hong Kong and SHPHK co-organised a vaccination training, namely the Hong Kong Pharmacist Vaccinators' Training Pathway and Programme (HKPVTPP). The aim of the training is to equip Hong Kong Pharmacists with essential vaccination skills and techniques, so that they are confident and competent to provide flu vaccination service to the general public.

The HKPVTPP consists of three parts:

Part 1(a): Face-to-face Vaccination Training

- Pharmacists would learn how to administer subcutaneous injection, intramuscular injection and intranasal spray correctly.

Part 1(b): Basic Life Support and Medical Emergencies Training

- Pharmacists would learn how to perform cardiopulmonary resuscitation (CPR) correctly so that they could respond to emergency situation quickly e.g. fainting and anaphylaxis while conducting immunisation service.

Part 1(c): Online Training and Assessment

- Pharmacists who have completed the required online training and passed the assessment would receive a certificate signifying satisfactory completion of the Influenza Online Training component.

Part 2: Examination on Clinical Skills and Competencies

- Pharmacists would be assessed by Objective Structured Clinical Examination (OSCE) on techniques on intramuscular, subcutaneous and intranasal administration.

Part 3: Practice under the supervision of a qualified vaccinator

- Pharmacists who have successfully demonstrated satisfactory standard in immunisation i.e. successfully vaccinated three to five real patients in a practical clinical setting, would be signed off by the assessor.

SHPHK ZOOM Workshop Series

The Society aims to equip pharmacists and pharmacists-to-be with essential skills and knowledge they need to provide professional pharmacy services to the general public through the organisation of different seminars and workshops all year round.

In October, the Society conducted four ZOOM workshops on various topics (see the table below).

The Society would like to thank **Hon. Assoc. Prof. William Chui** (President of SHPHK), **Mr. Raymond Mak** (Senior Pharmacist (Clinical), Queen Mary Hospital), **Miss Tammy Chan** (Clinical Pharmacist, Queen Mary Hospital), **Ms. Sau Chu Chiang** (Advisor of SHPHK) and **Mr. Michael Ling** (Advisor of SHPHK) for delivering the online workshops to our members and pharmacy students.

More educational activities to come in 2021! Watch this space!

SHPHK Activities: 2020 In Review

April	1. Webinar: The role of ICS in COPD care
May	2. Webinar: A Frontline Perspective on Implementing Preferred Reliever
June	3. SHPHK Annual General Meeting
	4. Webinar: Exploring the Potential of Biotherapies: Totality of Evidence for ABP 980
August	5. Public Hospital Pharmacist Virtual Roundtable Meeting: Emergence of Biosimilars and Their Impact on Hong Kong Healthcare System
September	6. Webinar: Cough, Cough Variant Asthma and Asthma
	7. Webinar: Revisiting Real-World Evidence of Panitumumab in RAS Wild-Type mCRC
	8. Vaccination Training and OSCE
October	9. SHPHK Zoom Workshop 1: The Roles of Pharmacists during COVID-19 and A Quick Update on the Development of Clinical Pharmacy & Pharmacy Specialisation in Hong Kong
	10. SHPHK Zoom Workshop 2: Bridging the Unbridgeable: The Paradigm Shift in Pharmacy Profession
	11. SHPHK Zoom Workshop 3: Attitudes You Should Master When You Step into a New Role
	12. SHPHK Zoom Workshop 4: Update on What We Know So Far about COVID-19 and its Treatment

SHPHK Membership Update

LEXICOMP is back!

You can now subscribe to the SHPHK three-year membership package to enjoy FREE access to LEXICOMP (from Jan 2021 to Dec 2023), on a first come first served basis. If you appreciate the work of SHPHK and wish to participate in the activities organised by SHPHK in the coming year, join us as member today! We look forward to working with you to promote, improve and assist the advancement of pharmaceutical care in Hong Kong!

As 2020 comes to an end, the Committee of SHPHK would like to take this opportunity to thank its Members for their continuous support to the Society.

Stay healthy, stay safe, and we wish you all Merry Christmas and a Happy New Year!

You are most welcome to follow the Society's Facebook page (@SHPHK) to know more about the Society's development and activities. You may also visit the Drug Education Resources Centre (DERC) Website: www.derc.org.hk to keep abreast of the latest news and development of pharmaceutical services in Hong Kong. Join us now as new member or renew your membership at the Society's website: www.shphk.org.hk.

RELPAX® Tablets 20mg
(Viatris)

Active Ingredient:
Eletriptan

Presentation:
Each RELPAX Tablet for oral administration contains 24.2 mg of eletriptan hydrobromide equivalent to 20 mg of eletriptan.

Pharmacological Properties:
Eletriptan is a selective 5-hydroxytryptamine 1B/1D (5-$HT_{1B/1D}$) receptor agonist. Eletriptan binds with high affinity to 5-HT_{1B}, 5-$HT1_{D}$ and 5-HT_{1F} receptors, has modest affinity for 5-HT_{1A}, 5-HT_{1E}, 5-HT_{2B} and 5-HT_{7} receptors. The therapeutic activity of RELPAX for the treatment of migraine headache is thought to be due to the agonist effects at the 5-$HT_{1B/1D}$ receptors on intracranial blood vessels (including the arteriovenous anastomoses) and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

Indications:
RELPAX is indicated for the acute treatment of migraine with or without aura in adults.

Dosage & Administration:
Dosing Considerations
Use only if a clear diagnosis of migraine has been established.

Perform a cardiovascular evaluation in triptan-naïve patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving RELPAX.

For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first RELPAX dose in a medically-supervised setting and performing an ECG immediately following administration of RELPAX. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of RELPAX.

Monitor blood pressure in patients treated with RELPAX.

Recommended Dose and Dosage Adjustment
The maximum recommended single dose is 40 mg. In controlled clinical trials, single doses of 20 mg and 40 mg were effective. If migraine has not resolved by 2 hours after administration, or returns after transient improvement, a second dose may be administered at least 2 hours after first dose. The maximum daily dose should not exceed 80 mg. Safety of treating an average of more than 3 migraine attacks in a 30-day period has not been established.

Dose adjustments due to adverse reactions
Discontinue Relpax if life-threatening disturbances of cardiac rhythm occur.

Drug Interaction
RELPAX should not be used within 72 hours with drugs that have demonstrated potent CYP3A4 inhibition, nor within 24 hours of another 5-HT_1 agonist, ergotamine-containing medication, or ergot-type medication. Serotonin syndrome may occur with RELPAX, particularly during co-administration with SSRIs, SNRIs, TCAs, and MAO inhibitors.

Hepatic impairment
No dose adjustment is necessary in subjects with mild or moderate hepatic impairment. RELPAX is not recommended for use in patients with severe hepatic impairment.

Renal Impairment
There was no significant change in clearance observed in subjects with mild, moderate or severe renal impairment, though blood pressure elevations were observed in this population.

Administration
RELPAX can be taken with or without food.

Overdosage
The elimination half-life of eletriptan is about 4 hours, therefore monitoring of patients after overdose with eletriptan should continue for at least 20 hours or longer while symptoms or signs persist.

Forensic Classification:
P1S1S3

Reference: **1.** Relpax® (eletriptan) Prescribing Information. Pfizer Upjohn Hong Kong Limited: Version March 2019 **2.** Drug Office. Search drugs database. Updated Dec 4, 2020. Accessed Dec 10, 2020. Available at: https://www.drugoffice.gov.hk/eps/drug/productDetail/en/consumer/128078

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