

HONG KONG PHARMACEUTICAL *JOURNAL*

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Rx

News & Short Communications

Integrating Self-Care in the Healthcare System:
The Crucial Role of Pharmacists

Pharmacological Treatment of Neuropathic Pain
(2 CE Units)

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Summary Report on the Hong Kong Pharmacy
Conference (February 27-28, 2016)

The Society of Hospital Pharmacists of Hong Kong
(SHPHK) Office Bearers 2016/17

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Hong Kong Pharmaceutical Journal: For Detailed
Instructions for Authors



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

Looking ahead – The development of the Pharmacy Profession in Hong Kong



The 2016 Hong Kong Pharmacy Conference was held from 27-28 February 2016. It was attended by a breaking record of over 650 participants. The 2016 Pharmacy Conference had two main goals: to reconnect with the scientific roots of pharmacy practice and to imagine how advances in science and technology could be harnessed to elevate the standard of practice characteristic of an advanced economy. A summary report, written by Professor Vincent Lee, Chairman of the Pharmacy Conference is printed on page 24. At the conference, there was a plenary session devoted to updates by representatives of the Task Force on Developing a Proposal in Establishing a Pharmacy Council in Hong Kong.

Since 1980's, the notion of establishing a pharmacy council in Hong Kong was discussed on and off for many years. The then Medical & Health Department realized the need to change the Pharmacy and Poisons Ordinance (PPO) and drafted 3 ordinances to regulate pharmacists, pharmaceutical products, and non-medicinal poisons. The project was revived in 1996 with two proposed ordinances: one for regulation of pharmacists and the other for regulation of pharmaceutical products and non-medicinal poisons. In 1998, a final draft of both ordinances was submitted to Health, Welfare, and Food Bureau. However, the legislative slot was taken up by a competing ordinance to revamp the then Urban Council.

During the Pharmacy and Poisons Amendment Bill 2014 legislative exercise, several leaders in pharmacy voiced the need to form a Pharmacy Council to regulate and oversee the development of the pharmacy profession, to issue code of practice for pharmacists, to register pharmacists and to determine the continuing education requirement, and to take disciplinary action against misconducts by pharmacists. With this background, a task force on developing a proposal in establishing a Pharmacy Council in Hong Kong was formed. An Update on the Pharmacy Council, written by Prof. Vincent Lee can be found on page 9.

The Pharmacy and Poisons Board of Hong Kong (PPBHK) announced on 4 January 2016 that it had become the 47th Participating Authority of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) with effect from January 1, 2016. (See page 5). The PIC/S is an international organisation comprising pharmaceutical inspection authorities around the world with a mission to lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products. As of January 1, 2016, there were 48 participating authorities in the PIC/S. In Hong Kong, all pharmaceutical manufacturers must obtain a licence from the PPBHK to produce medicines. One of the key requirements for licensing a pharmaceutical manufacturer is the full compliance with the PIC/S GMP standards. For the local manufacturers, they must employ an authorized person. Since June 2015, authorized persons must apply to the PPB to be listed on the Register of Authorized Persons. Currently, the authorized persons of the GMP manufacturers with a full license are registered pharmacists in Hong Kong that have at least 3 years of GMP experience in quality assurance/quality control. The role of the authorized person is to ensure that medicines are manufactured in accordance to GMP standards and meet the specifications before release to the market. More local pharmacist graduates are going into the local pharmaceutical manufacturers to learn about the manufacturing of drugs.

A great majority of our pharmacists are currently working in the Public Hospitals in the Hospital Authority. The pharmacists in the public and private hospitals dispense drugs to out patients and also provide individual patient dispensing service to all clinical wards, provide drug information service to all healthcare professionals, replenish ward medication stock periodically, and provide patient educational programme. In some of the HA Hospitals, pharmacists constitute TPN, conduct medication reviews, provide information to doctors and patients on oncology drugs, pediatric drugs, etc. With the complexity of innovative drugs, the need for specialist pharmacists emerge. The HA has also planned on enhancement of Pharmacy Services in the years to come.

In the article written by BESANÇON, Luca on page 13: Integrating Self-Care in the Healthcare System: The Crucial Role of Pharmacists, it stated that pharmacists are an integral component in every healthcare system due to their various roles in providing pharmaceutical care, in particular the self-care of patients. This article illustrates how pharmacists could promote responsible use of medicines in the community and act as an entry gate to the healthcare system for patients.

Currently, there are about 600 pharmacies in Hong Kong and without the separation of Prescribing and Dispensing, there is insufficient prescriptions for the community pharmacies in Hong Kong. In the past few years, the chain stores have done a lot of work to promote the images of pharmacists. Patients are encouraged to seek the advice of pharmacists on their medications and also health products. With the aging population, the public hospitals are flooded with patients. The Health, Welfare and Food Bureau has initiated Public Private Programmes starting with private doctors. The Tin Shui Wai Primary Care Partnership Project has been launched to test the use of public-private partnership model and supplement the provision of public general out-patient services in Tin Shui Wai. Under this programme, eligible patients in Tin Shui Wai who have been under the care of HA's existing Tin Shui Wai GOPC are invited to participate. Those who choose to participate in this programme may enroll with a private doctor in Tin Shui Wai who participates in this programme. They may seek up to 10 medical consultations with the private doctors, and are required to pay a standard fee of \$45 per consultation, the same fee as attending HA's GOPCs.

The General Outpatient Clinic Public Private Partnership (GOPC Partnership) Programme aims to enhance the provision of primary care services by providing choice to patients for receiving primary care services from the private sector. It also helps promote the family doctor concept. Initially, clinically stable patients having hypertension with or without hyperlipidemia, and later diabetes patients, currently taken care of by HA GOPCs will be invited for voluntary participation. The GOPC Partnership Programme will initially be piloted in Kwun Tong, Wong Tai Sin and Tuen Mun. Each participating patient will receive up to 10 subsidised visits per year, including medical consultations covering both chronic and acute care. Under the GOPC Partnership Programme, participating patients only need to pay the HA GOPC fee of \$45 (as per Gazette) for each consultation.

With the aging population and the burden on public hospital, I can envisage that the PPP programme can be extended to community pharmacies and pharmacists. There are qualifying criteria and logistics to work out. I sure hope that our professional leaders and community pharmacists will take this opportunity to expand their role in dispensing of drugs, counselling of patients and promote responsible use of medicines in the community.

Cheng Mary Catherine
Managing Editor
29th April 2016

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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
- OTC & Health
- Medication Safety
- Society Activities
- Drugs & Therapeutics
- Pharmaceutical Techniques & Technology
- Herbal Medicines & Nutraceuticals
- 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:

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Pharmacy and Poisons Board of Hong Kong accedes to Pharmaceutical Inspection Co-operation Scheme

Date: January 4, 2016

The Pharmacy and Poisons Board of Hong Kong (PPBHK) announced on 4 January, 2016 that it had become the 47th Participating Authority of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) with effect from January 1, 2016.

The PIC/S is an international organisation comprising pharmaceutical inspection authorities around the world with a mission to lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products. As of January 1, 2016, there were 48 participating authorities in the PIC/S.

In Hong Kong, all pharmaceutical manufacturers must obtain a licence from the PPBHK to produce medicines. One of the key requirements for licensing a pharmaceutical manufacturer is the full compliance with the PIC/S GMP standards. The Drug Office of the Department of Health (DH) provides licensure support to the PPBHK and conducts GMP inspections to ensure compliance.

The PPBHK considers that its accession to the PIC/S signifies the recognition of its GMP inspectorate and the pharmaceutical trade by international drug regulatory authorities. The PPBHK is

confident that medicines produced in Hong Kong are on par with international standards.

In 2009, the former Review Committee on Regulation of Pharmaceutical Products in Hong Kong recommended the DH to upgrade the licensing standards of local drug manufacturers to the PIC/S GMP standards. GMP is a quality assurance approach used by the drug manufacturing industry to ensure that products are consistently produced and controlled throughout the manufacturing process. In the past few years, both the Drug Office of the DH and local pharmaceutical manufacturers have been putting tremendous efforts to attain a higher GMP standard. Subsequently, the PPBHK adopted the PIC/S GMP as one of the licensing conditions for local manufacturers with effect from October 1, 2015.

Following the PPBHK's application for accession to the PIC/S, an audit team established by the PIC/S visited Hong Kong in January 2015 to evaluate the drug regulatory system and GMP inspection standards of Hong Kong. The PIC/S then considered that the regulatory standards of Hong Kong complied with its requirements and accepted the PPBHK as the 47th Participating Authority with effect from January 1, 2016.

Source: www.drugoffice.gov.hk

Anticholinergics Do Not Increase Risk of Dementia, Study Finds

Date: January 5, 2016

There has been a recent claim that regular use of anticholinergic drugs, which are extensively used for treating bladder dysfunction, mood disorders, and pain, will lead to a greater risk of developing dementia, in particular patients with Alzheimer's disease (AD). Since these drugs are commonly prescribed in patients with Parkinson's disease (PD), meanwhile those drugs can also be available without prescription, this increase in risk of dementia becomes a cause for concern. However, a study in the current issue of the Journal of Parkinson's Disease showed the association was ungrounded.

The investigator from the Newcastle University said it was pioneer study to inquire the relationship between "anticholinergic burden and mild cognitive impairment (MCI) in PD participants", and was "timely given recent research demonstrating cumulative anticholinergic burden and risk of AD in the general population."

195 PD patients and 84 control patients were studied, adopting data from the Incidence of Cognitive Impairment in

Cohorts with Longitudinal Evaluation – Parkinson's Disease study. The detailed medication history of the PD patients was evaluated based on the Anticholinergic Drug Scale (ADS). Using a scale from 0 to 3, each drug item was classified according to no (0), mild (1), moderate (2), or high (3) anticholinergic activity. Total usage from baseline to 18-month follow up was used to generate a total burden score. Subjects with ADS scores equal to 0 were designated PD-ADS group while those with ADS scores larger than or equal to 1 were in the PD+ADS group.

Comparing the PD-ADS (n = 112) and PD+ADS (n = 83) groups, there were no differences in patients' attention, memory, and executive function in assessments at 18 months. The proportion of MCI was similar in the two groups, suggesting that the association between anticholinergic drug use and dementia may be far-fetched.

Source: www.journalofparkinsonsdisease.com

Metformin Improves Insulin Sensitivity in Non-diabetic Pregnant Women

Date: January 28, 2016

Metformin is commonly prescribed as an anti-diabetic agent in Type II Diabetes. A recent study finds that metformin improves insulin sensitivity in patients as it leads to less weight gain.

A total of 50 women withdrew consent during the trial, which left 202 women in the metformin group and 198 in the placebo group. There was no significant between-group difference in the median neonatal birth-weight z score. The median maternal gestational weight gain was lower in the metformin group than in the placebo group (4.6 kg [interquartile range, 1.3 to 7.2] vs. 6.3 kg [interquartile range, 2.9 to 9.2], $P < 0.001$), as was the

incidence of preeclampsia (3.0% vs. 11.3%; odds ratio, 0.24; 95% confidence interval, 0.10 to 0.61; $P = 0.001$). However, the incidence of side effects was also higher in the metformin group than in the placebo group.

In conclusion, for non-diabetic pregnant women who had a BMI of more than 35, the antenatal administration of metformin reduced maternal weight gain but not neonatal birth weight, but side effects should be monitored.

Source: www.nejm.com

Antidepressants May Double the Risk of Aggression and Suicide in Children

Date: January 28, 2016

Children and adolescents have a doubled risk of aggression and suicide when taking one of the five most commonly prescribed antidepressants, according to the findings of a study published in *The BMJ*.

A team of researchers from Denmark carried out a systematic review and meta-analysis of 68 clinical study reports of 70 trials with 18,526 patients to examine use of antidepressants and associated serious harms, such as deaths, suicidal thoughts and attempts as well as aggression and akathisia, a form of restlessness that may increase suicide and violence.

They examined double blind placebo controlled trials that contained patient narratives or individual patient listings of associated harms and compared the results from the clinical study reports with data from individual patient listings or narratives of adverse effects. This revealed misclassification of deaths and suicidal events in people taking antidepressants. For example,

four deaths were misreported by a pharmaceutical company, in favour of the antidepressant.

In summary trial reports of the drug company Eli Lilly, almost all deaths were noted, but suicidal attempts were missing in 90% of instances, and information on other outcomes was incomplete. These were "even more unreliable than we previously suspected," write the authors.

Researchers recommend "minimal use of antidepressants in children, adolescents, and young adults, as the serious harms seem to be greater, and as their effect seems to be below what is clinically relevant," and suggest alternative treatments such as exercise or psychotherapy. They also call for the need to identify "hidden information in clinical study reports to form a more accurate view of the benefits and harms of drugs."

Source: www.bmj.com

Antenatal Betamethasone May Help Prevent Respiratory Complications

Date: February 4, 2016

Antenatal glucocorticoids are widely used for pregnancies at risk for early preterm delivery (before 34 weeks). It is found to reduce adverse neonatal outcomes, including death, respiratory distress syndrome and other complications. However, birth in late preterm period (34 to 36 weeks) is more common and have more complications for newborns than birth at term (37 weeks or later).

A multi-centered, randomized trial was conducted to assess whether betamethasone can decrease respiratory and other neonatal complications for late preterm delivery. 2831 women with a singleton pregnancy (34 to 36 weeks of gestation) and high probability of delivery in the late preterm period were analyzed. They were randomly assigned in a 1:1 ratio to a course of two intramuscular injections containing either 12 mg of betamethasone (equal parts betamethasone sodium phosphate and betamethasone acetate) or matching placebo administered

daily. The need for respiratory support was the primary outcome while respiratory complications newborns and maternal inflammation were the main secondary outcomes.

Compared with the control, the betamethasone group had a lower need for respiratory support (relative risk of 0.80, $P = 0.02$) and a lower rate of severe respiratory complications (relative risk of 0.67, $P < 0.001$). Incidence of intra-amniotic infection or endometritis, rates of cesarean delivery, time to delivery, and length of stay were also similar in the two groups

To conclude, the administration of antenatal betamethasone in women at risk for late preterm delivery significantly reduced the rate of respiratory complications in newborns.

Source: www.nejm.org

New Front Opens in the Battle Against Stroke

Date: February 17, 2016

Treatment of insulin resistance is potentially a new preventive strategy adding to the standard care after an ischemic stroke or a transient ischemic attack (TIA). Pioglitazone, a drug within a class of medication thiazolidinediones, which can increase insulin sensitivity hence reducing insulin resistance, was shown to lower the risk of stroke or heart attack in patients who had previously suffered from a stroke.

Insulin resistance is almost universal in type 2 diabetic patients, but it is also present in more than 50% non-diabetic patients who have had an ischemic stroke or a TIA. Insulin resistance increases the risk of vascular diseases, possibly because of associated hypertension, hyperglycemia, hyperinsulinemia, dyslipidemia, and endothelial dysfunction, etc.

In this five-year, double-blind trial of pioglitazone versus a placebo, the eligible patients were at least 40 years old, had

insulin resistance, and had had an ischemic stroke or a TIA during the 6 months before randomization. Diabetic patients were excluded. It was found that patients receiving the drug (175 of 1939; 9.0%) had 24% lower incidences of either stroke or myocardial infarction than the placebo group (228 of 1937; 11.8%). The incidence of a new diagnosis of diabetes was also lower in the pioglitazone group (3.8%) than the placebo group (7.7%).

Currently, use of pioglitazone in non-diabetic patients is not FDA-approved. This study demonstrated that pioglitazone can potentially prevent cardiovascular events in patients who have cerebrovascular diseases with insulin resistance.

Source: www.nejm.org

Low-dose Hydrocortisone Improves Survival in Extremely Premature Infants

Date: February 22, 2016

Bronchopulmonary dysplasia is a major cause of neonatal mortality after extremely premature birth and has few treatment options. A pilot study has showed that hydrocortisone improved survival in infants, but strong evidence from large clinical trials to support postnatal steroid use is still limited.

A study was conducted in France to investigate whether low-dose hydrocortisone would improve bronchopulmonary dysplasia-free survival in extremely premature infants. The double-blind, placebo-controlled, randomised trial was performed at 21 French tertiary-care neonatal intensive care units. Extremely preterm infants participated in this study were born at less than 28 weeks of gestation. After screening 1072 neonates from May 2008 to January 2014, 255 and 266 infants were randomly assigned to hydrocortisone and placebo (glucose) respectively. Within the first 24 hours of life, the hydrocortisone group received intravenous hydrocortisone hemisuccinate 1 mg/kg divided into two doses per day for 7 days, then one dose of 0.5 mg/kg per day for 3 days.

The hydrocortisone group showed 60% bronchopulmonary dysplasia-free survival at 36 weeks of postmenstrual age,

which was greater than the 51% of the placebo group ($p=0.04$). The hydrocortisone group also showed earlier extubation. The proportion of extubated patients within the first 10 postnatal days in the hydrocortisone group was 60%, compared to 44% of the placebo group ($p = 0.0002$). In addition, a smaller proportion of patients received patent ductus arteriosus ligation in the hydrocortisone group (15%) than the placebo group (21%) ($p=0.03$). Nonetheless, the hydrocortisone group showed a higher rate of sepsis in infants born at 24–25 weeks gestational age (40% vs 23%, $p=0.02$). There was no significant difference in the occurrence of potential severe adverse events, including pulmonary haemorrhage and gastrointestinal perforation, between the two subgroups.

In sum, low-dose hydrocortisone initiated within 24 hours after birth and continued for 10 days increased the rate of bronchopulmonary dysplasia-free survival in premature infants. An ongoing follow-up study at a corrected age of 18–22 months will further examine the effects of this treatment and its potential use as a prophylaxis for bronchopulmonary dysplasia.

Source: www.thelancet.com

Study Doubts an Antiplatelet as Analgesic in Sickle Cell Anemia

Date: February 23, 2016

A trial conducted in 13 countries showed that adenosine diphosphate-directed antiplatelet agent prasugrel had no significant effect in reducing pain associated with vasoocclusive crises in sickle cell anemia when compared with placebo.

In this phase 3 double-blind, placebo-controlled, multinational trial, 341 children and adolescents aged 2 to 17 years with sickle

cell anemia were randomly assigned into two equal groups, one receiving oral prasugrel and one receiving placebo over 9 to 24 months. The primary end point – the rate of vasoocclusive crises did not differ significantly between the prasugrel group (67.3%) and the placebo group (72.4%). There were also no significant differences in the rate and intensity of sickle-cell related pain (secondary end points) and adverse effects

It was suggested that the ineffectiveness of prasugrel might be due to lower than anticipated level of platelet inhibition. Therefore, higher doses of antiplatelet agents or combination therapy with other drugs might be beneficial. Besides, the number

of vasoocclusive crises was smaller in 12 years and older patients in the prasugrel group, suggesting that platelet activation might be more important in older patients.

Source: jama.jamanetwork.com

Trimethoprim–Sulfamethoxazole Still Effective for Uncomplicated Skin Abscess

Date: March 3, 2016

Amid the rampant growth of methicillin-resistant *Staphylococcus aureus* (MRSA), there is a looming concern about the effectiveness of the conventional uncomplicated skin abscess treatment with Trimethoprim and Sulfamethoxazole.

This led to a randomized trial at five emergency departments in the US. It aimed to determine whether trimethoprim–sulfamethoxazole (at doses of 320 mg and 1600 mg, respectively, twice daily, for 7 days) would be superior to placebo group who had an uncomplicated abscess treated with drainage. In the trial, 45.3% of patients had wound cultures positive for MRSA. Participants with positive MRSA in wounds were divided into two groups: the trimethoprim–sulfamethoxazole group (630) and the placebo group (617). The study primarily compared the rate of clinical cure of the abscess, subsequent surgical drainage procedures, skin infections at new sites and infections in household members.

7 to 14 days after the treatment period, the treatment group had a higher cure rate (80.5%, i.e. 6.9% higher) than the placebo group (73.6%). Meanwhile, trimethoprim–sulfamethoxazole was superior to placebo with respect to most of the secondary outcomes. The treatment lowered the rates of subsequent surgical drainage procedures (5.2% less), skin infections at new sites (7.2% less) and infections in household members (2.4% less). Both groups had the same percentage of patients developing invasive infection (0.4%). All the comparisons fitted the 95% confidence interval [CI].

In sum, the combined use of Trimethoprim and Sulfamethoxazole is still effective in curing patients with drained cutaneous abscess than placebo despite growing resistance.

Source: www.nejm.org

Fosaprepitant: A Potential Anti-emetic in Chemoradiotherapy

Date: March 4, 2016

Currently, randomized studies on prophylaxis for nausea and emesis induced by radiotherapy are rare. According to literature search by the research group, no related studies have been done on concomitant chemoradiotherapy and on the prophylactic role of neurokinin-1 (NK-1) receptor antagonists in radiotherapy.

The research group has initiated the first randomised, double-blind, placebo-controlled phase 3 trial to investigate the efficacy and safety of adding a NK-1 receptor antagonist, fosaprepitant, to palonosetron and dexamethasone, in the prevention of nausea and emesis induced by fractionated radiotherapy and concomitant weekly cisplatin in cervical cancer patients. Between June 2010 and March 2015, 234 patients from four countries (Germany, Australia, Norway, and Denmark) were randomly assigned to receive a single dose of fosaprepitant 150 mg (118) or placebo (saline) (116) by intravenous infusion, in combination with intravenous palonosetron 0.25 mg and oral dexamethasone 16 mg before cisplatin (40 mg/m²) administration. In addition, all patients received dexamethasone orally according to the schedule of 8 mg twice a day on day 2, 4 mg twice a day on day 3, and 4 mg once on day 4. The treatment was given weekly for five weeks.

The proportion of patients with sustained no emesis after 5 weeks of treatment was 65.7% for the fosaprepitant group (95% CI 42.2–89.2) and 48.7% for the placebo group (25.2–72.2). The fosaprepitant group showed a significantly lower cumulative risk of emesis compared with the placebo group (subhazard ratio 0.58; p=0.008). Few grade 3 adverse events were recorded in both subgroups. The most common grade 3 adverse event was diarrhea, observed in 9% patients in the fosaprepitant group and 5% patients in the placebo group. One grade 4 adverse event was reported – neutropenia in the fosaprepitant group. No deaths occurred in both groups.

The study has provided new insight of administering fosaprepitant in combination with palonosetron and dexamethasone in the prophylaxis for nausea and emesis in concomitant chemoradiotherapy. Further studies should assess this combination in other radiotherapy settings with or without concomitant chemotherapy.

Source: www.thelancet.com

Update on the HK Pharmacy Council

Among the challenges facing Hong Kong is access to a robust and resilient healthcare delivery system to meet the rising demand for chronic disease management affecting the elderly population. What has long been a physician-centered, supply-driven model of care is capturing the cautious embrace of patients as well as public health officials for a patient-centered, demand-driven model of care. Conceivably the public may partner with community pharmacists in between physician visits to use technology in coordinating care as relates to drug adherence and progress of drug therapy.

Drugs have played a prominent role in the dramatic rise in life expectancy in the 20th century. Today, drugs are more powerful, expensive, and demanding a comprehensive understanding of the complexity inherent of multiple drug therapy to ensure the best possible clinical outcome. Indeed, pharmacist intervention has been credited with reducing the incidence of avoidable adverse drug reactions worldwide.

Yet the pharmacists in Hong Kong have been underutilized in their professional role. Because of understaffing due to budgetary constraints and a small annual output of pharmacist graduates, pharmacists are tied to their dispensing role at the expense of a clinical patient-centered role. Recent years have witnessed an emerging consensus among the leadership of mainstream pharmacist professional organizations that a pharmacy council with responsibility on par with the medical council, nursing council and Chinese medicine council is the right statutory body to set professional standards for the pharmacy profession and self-regulate pharmacists. Moreover, the future pharmacy council may serve as a bridge to other health related councils in the collective commitment to improve the efficiency of the health-care system in Hong Kong by implementing shared care. By speaking out on pharmacist manpower and pharmaceutical care, the council is the potential regulatory body that could make an impact in enhancing drug safety and delivery of the care that only the pharmacists are educated for and are capable of delivering to the public.

Dated as far back as 1981, the notion of establishing a pharmacy council in Hong Kong was discussed on and off for the ensuing three decades. The impetus for change was the realization by both the Pharmaceutical Society and the then Government Medical and Health Department that the Pharmacy and Poisons Ordinance (PPO) was too complicated, too confusing, and too encompassing in the portfolio of items and matters under its purview --- from quality and safety of pharmaceutical products to registration and discipline of pharmacists. The original decision was to have 3 ordinances to separately regulate pharmacists, pharmaceutical products, and non-medicinal poisons. The three draft ordinances were produced by the Medical and Health Department in 1986, approved by the Pharmacy and Poisons Board (PPB), and released for consultation among the various stakeholders in 1987, but there was no follow up action from the PPB secretary. The project was revived in 1996 with two proposed ordinances: one for regulation of pharmacists (where “pharmacy council” as a statutory body was mentioned throughout the draft) and the other ordinance for regulation of pharmaceutical products and non-medicinal poisons. In 1998, in accordance with the requirements of the Government Department of Justice, draft drafting instructions for both ordinances was submitted to the then Health, Welfare, and Food Bureau for legislative approval. Regrettably, the project was put on hold due to the Government’s

more pressing need to enact legislation to revamp the functions of the then Urban Council, Regional Council, Urban Services Department and Regional Services Department.

A two decade-long hiatus followed. Pharmacy reform in the name of separation of prescribing and dispensing was at center stage. It was not until the Pharmacy and Poisons Amendment Bill 2014 legislative exercise that the leaders in mainstream pharmacy organizations voiced the pressing need to establish a Pharmacy Council under law:

1. To regulate and oversee the development of the pharmacy profession,
2. To issue a code of practice for pharmacists,
3. To register pharmacists and to determine the continuing education or continuing development requirement for re-licensure, and
4. To take disciplinary action against misconduct by pharmacists.

Against this backdrop the “Task Force on Preparation of a Proposal for Establishing a Pharmacy Council”, comprising more than 20 pharmacist representatives from various practice sectors, was established in October 2014. As a prelude to establishing a framework for the future Hong Kong Pharmacy Council (HKPC), the Task Force systematically studied the vision, mission, governance, and laymen representation of various health councils all over the world. Of those councils, the task force eventually focused on three: the Hong Kong Medical Council, the Hong Kong Nursing Council, and the General Pharmaceutical Council of Great Britain. They were selected as being most relevant according to our SWOT analysis (**Figure 1**).

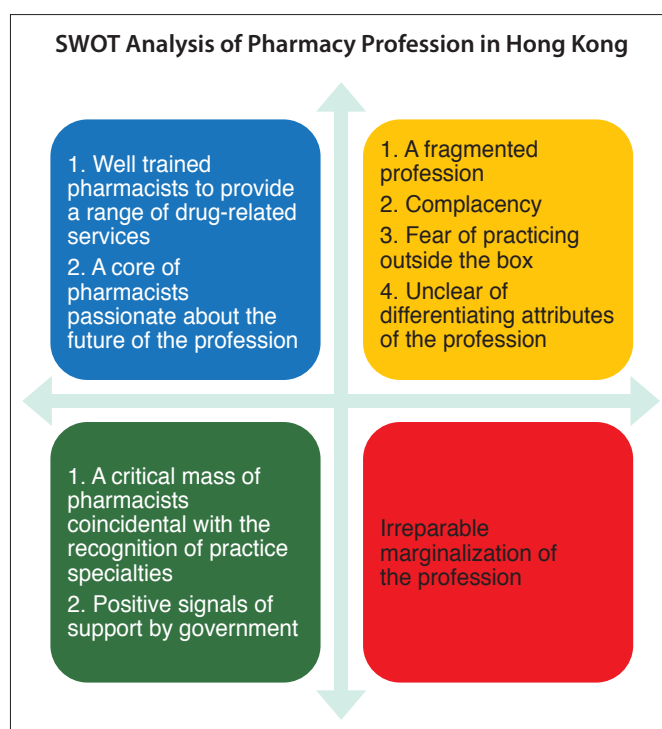


Figure 1

Simply put, HKPC aspires to be an independent statutory body dedicated to continuous quality enhancement of professional practice across all sectors of the pharmacy profession in Hong Kong. Its mission is to promote health, ensure drug safety, and protect the well-being of the public by establishing standards consistent with safe and effective practice of pharmacy.

Towards that end, the Council will serve several functions:

1. To set standards for safe and effective pharmacy practice;
2. To set standards and accredit Bachelor of Pharmacy programs (or entry pharmacy degree programs), internship training programme, and continuing professional development or continuing education programmes;
3. To set standards for the registration of specialist pharmacists and accredit programmes of specialties in pharmacy and pharmaceutical sciences;
4. To provide a platform for promoting interactions with other healthcare professionals;
5. To set standards of Licensing Examinations and to be responsible for the conduct of such examinations;
6. To ensure the continued fitness to practice of registrants;
7. To exercise the regulatory and disciplinary powers for the profession; and
8. To publish or provide information about the
 - a. regulation of pharmacists, for example, by establishing a Code of Practice
 - b. guidance to registrants, employers and other persons concerned in respect of the standards for the education, training, supervision and performance of non-registrants who are involved in the provision of pharmacy service

In turn the following committees or subcommittees will be established to carry out HKPC's functions:

1. Registration Committee
 - a) Licentiate Sub-Committee: to be responsible for the licensing of pharmacists,
 - b) Examination Sub-Committee: to set up and conduct examinations for registration of pharmacists,
 - c) Pharmacy Internship Sub-Committee: to set standards and regulate internship training programs for interns,
 - d) Continuing Education Sub-Committee: to define the Continuing Professional Development (CPD) and Continuing Pharmacy Education (CPE) requirements.
2. Accreditation and education Committee: to be responsible for accreditation of local pharmacy programs,
3. Disciplinary Committee
 - a) Preliminary Investigation Sub-Committee
 - b) Fitness to Practice Sub-committee

4. Appeal Tribunal.

We estimate that 75% of the Council activities will be devoted to registration, 10% each on setting standards and accrediting educational programs, and only 5% on activities related to discipline and appeal. As a result of misinformation by society leadership, there was fear among a few pharmacists from the rank and file that the primary function of HKPC was disciplinary. That clearly is not true.

The preliminary framework of HKPC, as outlined above, was presented and discussed in the final plenary session of the 2015 Pharmacy Conference. It was well received, thereby motivating the Task Force to continue its deliberation on logistics matters like composition of the Council, registration fee, requirement of continuing education, and reporting and handling of complaints. While there was consensus that both pharmacists and laymen should be represented on the council, the ratio between the two is still under active discussion. Neither is there a resolution on the participation of laymen in every committee or subcommittee of the Council.

As to whether there will be an increase in registration fee, it is too early to tell. Historically, both the Hong Kong Medical Council and the Hong Kong Nursing Council are fully funded by the Hong Kong SAR government. Unless this funding model is modified in the future, the Hong Kong Pharmacy Council should also be fully funded by government.

The latest version of the Council composition being considered is a Council of 7 registered pharmacists and 5 laymen. The composition of pharmacists will be determined essentially by practice sector: 3 by nomination and 4 by election. This streamlined structure is necessary for making timely decisions in today's fast paced world. The sectors are hospital, community, industry, academia, and regulatory. The College of Pharmacy Practice and the Academy of Pharmacy will each have a seat on the Council to champion for pharmacist specialists. To facilitate communication with government, the Chair of the Pharmacy and Poisons Board and the Head of the Drug Office will be ex officio members. To facilitate communication with key partners, the President of the HK Medical Council and the President of the HK Nursing Council will be invited as ex officio members as well.

Since November 2015, the Task Force had conducted a marathon of consultations with every sector in pharmacy practice as well as meetings with various stakeholders, including patient groups, legislative council members, a member of the nursing council, and the Permanent Secretary of Food and Health Bureau (Health) (**Table 1**). Altogether we were able to reach out to more than 300 pharmacists. We were gratified that all but one group was supportive of the plan to establish a Pharmacy Council in Hong Kong. Among the questions frequently asked were: Since the Pharmacy and Poisons Board seems to be doing a good job, why do we need a Pharmacy Council? What value would the Pharmacy Council add? How will the office be financed? As already hinted upon, the impact of establishing the Pharmacy Council on the registration fee is a complex matter with several interdependent variables subject to future negotiation.

Establishing a pharmacy council for Hong Kong is a welcomed sign of progress of the pharmacy profession in this vibrant city.

Consultations and Meetings

Nov 02, 2015	• Meeting with The Practising Pharmacists Association Of Hong Kong (PPA) and Hong Kong Pharmacists Union members
Nov 04, 2015	• Meeting with The Hong Kong General Chamber of Pharmacy Limited (HKGCP) members
Nov 10, 2015	• 1 st Consultation pharmacists from all sectors (110+)
Nov 18, 2015	• Consultation for BPharm students, CUHK (50+)
Nov 27, 2015	• Consultation for BPharm students, HKU (40+)
Dec 01, 2015	• Meeting with the Under Secretary for Food and Health, Dr. Sophia Chan and the Head of Healthcare Planning and Development Office, Mr. Chris Sun of Food and Health Bureau (FHB)
Dec 22, 2015	• Tea gathering - consultation for independent community pharmacists, Tsuen Wan District (20+)
Jan 14, 2016	• 2 nd Consultation for public and private hospital pharmacists (100+)
Jan 20, 2016	• Meeting with Legislative Council members, Dr LEUNG Ka Lau and Prof LEE Joseph
Jan 29, 2016	• Meeting with Chain-store community pharmacists (15+)
Feb 19, 2016	• Meeting with the Society for Community Organization
Feb 25, 2016	• Meeting with the Alliance for Patients' Mutual Help Organizations
Mar 31, 2016	• Meeting with a member of the Nursing Council
May 12, 2016	• Meeting with the Permanent Secretary of FHB (Health)

Table 1

It is not a repudiation of the historical role of the Pharmacy and Poisons Board. Rather, it is a statement to the public and other healthcare providers in Hong Kong that the pharmacy profession has reached maturity. Pharmacists are eager to look after the public's best interests in getting quality medicine as well as quality professional services only pharmacists have the knowledge and competency to provide. It is imperative that pharmacists in Hong Kong unite behind the vision and mission of the HK Pharmacy Council in planning. Those who can practice pharmacy at a level beyond dispensing now, resulting in improved user satisfaction and/or cost savings, should seize every opportunity to publicize the value pharmaceutical care can add to disease management. The best case scenario will be one whereby the public will be the champion of our profession and the Hong Kong Pharmacy Council. In the worst case scenario, our profession will continue to be ignored in policy decisions affecting our future were we reluctant to step outside of our comfort zone.

How wide is the gap between the vocal minority and the passionate majority? In my view, the two camps are closer than what the onlookers would imagine. Both camps had identified pharmacy reform and pharmacy council as priorities for Hong Kong pharmacists. It is the collective wisdom of the Task Force that the establishment of the Hong Kong Pharmacy Council will trigger a cascade of positive changes integral to pharmacy reform, spanning practice environment, professionalism, and integration of automation, robotics, and machine learning into the workflow.

Our success in establishing the pharmacy council will be contingent on the willingness of the entire pharmacy profession to close ranks and embrace change. The profession needs to be concerted in leveraging on the breathtaking technological

advances in the digital era to create a new brand of pharmacy practice. Dispensing is not enough to satisfy the expectations of a knowledge-savvy public. The new standard of pharmacy practice will be assuring the patient of the right drug at the right dose and dosing frequency indexed to the patient's stage of disease, co-morbidity, genetic factors, and life style. The profession must educate and demonstrate to the end user, the provider, and the payer that the pharmacist is the only healthcare professional who is educated and trained to manage therapeutic complexity in a cost-effective manner. Hospital pharmacists must set aside time to practice in the manner just described in high-risk patients, and community pharmacists must demonstrate to the patient that by filling his/her prescription in the community pharmacy will automatically trigger professional monitoring of progress of disease, efficacy, and possible emergence – as well as professional management – of troublesome side effects.

In the months ahead, the Task Force will finalize the composition of the Council, continuing education requirements for re-licensure, by-laws for conducting the business of the committees and subcommittees, budget and other matters that will be the draft proposal for establishing the Hong Kong Pharmacy Council. The other tasks include establishing a website and, with IT support, a Facebook account; expanding the circle of leadership; developing strategies to rally support by the public, patient groups, and healthcare providers; and reaching out to the task force of pharmacy reform.

In summary, establishing a HK Pharmacy Council is not only about aligning profession-wide practice standards with unmet needs in pharmaceutical care of the public. More importantly it is about the commitment of a young but maturing pharmacy profession to work collaboratively with the modernized healthcare team to improve patient outcome. It is about fulfilling the pharmacy profession's share in helping alleviate the stress on a heavily burdened healthcare system. Ultimately, it is about improving the quality of life and about saving lives.

Sincerely,



Prof. Vincent H.L. Lee
Chairman
Task Force on Preparation of a Proposal for
Establishing a Pharmacy Council in Hong Kong

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Integrating Self-Care in the Healthcare System: The Crucial Role of Pharmacists

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ABSTRACT

Pharmacists are an integral component in every healthcare system due to their various roles in providing pharmaceutical care, in particular the self-care of patients. This article illustrates how pharmacists could promote responsible use of medicines in the community and act as an entry gate to the healthcare system for patients. Participation of pharmacists in patient self-care is found to be remarkable and be implemented in a number of countries. Although there are different restrictions ahead, it is expected that pharmacy service can be evolved to play a more important role in primary care setting.

Keywords: *self-medication, healthcare system, health professionals, therapy management, pharmaceutical triage, non-prescription medicines*

INTRODUCTION

For many years, pharmacists have been involved in supporting self-care but, more recently, this role has been better demonstrated and thus recognised and valued by governments and patients.

The World Health Organization defines self-care in health as “the activities individuals, families and communities undertake with the intention of enhancing health, preventing disease, limiting illness and restoring health.” It also links these activities with the foundation of knowledge and skills from a pool of both professional and lay experience. It further mentions that these activities are “undertaken by lay people on their own behalf, either separately or in participative collaboration with professionals”,⁽¹⁾ of which pharmacists are probably the health professionals from whom people first seek in terms of self-care advice.

ROLE OF PHARMACISTS

In 2011, the International Pharmaceutical Federation (FIP) and the World Health Organization (WHO) adopted joint guidelines on good pharmacy practice: standards for quality of pharmacy services.⁽²⁾ This important document describes, among other things, four main roles of pharmacists as follows:

- *Role 1: To prepare, obtain, store, secure, distribute, administer, dispense and dispose of medical products.*

- *Role 2: To provide effective medication therapy management.*
- *Role 3: To maintain and improve professional performance.*
- *Role 4: To contribute to improvement of the effectiveness of the healthcare system and public health.*

For many years, Role 1 — dispensing — has been the main focus of our profession but we have been moving from a product-focused to a patient-centred approach. Through medication therapy management (Role 2), pharmacists turn pharmaceutical products into health solutions by adding services that ensure better therapeutic outcomes for individual patients. This also pushes our profession to rethink the types of services we deliver in conjunction with the dispensing of a non-prescription medicine. Such services can be before, during and/or after supply. These services can also be independent of the provision of a pharmaceutical product. Role 3 refers to the competencies required to perform any of the other roles. Most of these competencies are usually acquired during undergraduate education and training, but they are also developed throughout the professional life through continuing education or continuous professional development. This competency journey is crucial to support the development of new services in response to the current and future needs of the population, including in the field of self-care. Finally, Role 4 highlights that pharmacists do not work in isolation but they are an integral part of the healthcare system. This is particularly true with self-care.

RESPONSIBLE USE OF MEDICINES

Pharmacists, as a member of the healthcare team, and through their daily engagement and collaboration with patients, can support patients in their self-care activities. This support must be founded on the responsible use of medicines. In 2013, FIP defined this concept as follows:

- *That a medicine is only used when necessary and that the choice of medicine is appropriate based on what is proven by scientific and/or clinical evidence to be most effective and least likely to cause harm. This choice also considers patient preferences and makes the best use of limited healthcare resources.*
- *That there is timely access and availability of quality medicine that is properly administered and monitored for effectiveness and safety.*

- *That a multidisciplinary collaborative approach is used that includes patients and those in addition to health professionals assisting in their care.*

The use of medicines is an essential component of the prevention, treatment, and cure of diseases. Although medicines can be effective, they can be hazardous. They can also be unnecessarily costly unless they are used responsibly. The concept of responsible use of medicines not only applies to prescription-only medicines, but also to non-prescription medicines.

Pharmacists and pharmacies have great potential to support responsible self-medication; they support a continuum of access (through their long opening hours and accessibility), appropriate selection (through the recommendation of medicines) and use (through their counselling) of medicines. This naturally involves patients and is guided by legal and economic frameworks.

Responsible self-medication implies that the choice of non-prescription medicines (whether initiated by the patient or through a recommendation of pharmacist) is appropriate and evidence-based. For non-prescription medicines, patients are usually more empowered to influence or make a decision based on their own preferences. The second point of the FIP definition refers not only to a timely access to quality medicines, but also to the active engagement of pharmacists in providing medication instructions and monitoring the treatment outcomes on an individual basis for each patient.

The responsible use of medicines involves all key stakeholders, from consumers of medicines, to healthcare professionals, to policy makers, all of whom are responsible for availability and access to medicines. Through multidisciplinary collaboration, first and foremost with patients, but also with all relevant healthcare professionals, pharmacists are key to responsible use of medicines within healthcare systems.

PHARMACISTS AS PROFESSIONALS OF THE ENTRY GATES TO THE HEALTHCARE SYSTEM

If patients are really at the centre of healthcare systems, they will also decide where their health journeys will start.

When British and American citizens were asked if they had experienced a health issue over the past month, 200 (20%) stated that they had not; 800 (80%) stated that they had experienced a health issue. Of this group, 217 went to see a doctor.⁽³⁾ The remainder (583, i.e. 58%) may have tried to solve their health issues by themselves or with the help of other healthcare professionals (such as pharmacists). This demonstrates the huge untapped potential for community pharmacists to serve even more as an entry gate to the healthcare system.

We already know that on average, 13% of patients visiting a pharmacy will leave without buying a product. But this does not mean that they have not benefited from their visits.⁽⁴⁾ In the context of pharmacies acting as entry gates to the healthcare system, pharmacists perform pharmaceutical triage: an assessment of symptoms and needs of a patient, leading to a

prognosis and concluding with a clinical decision on whether to provide a safe, tailored-made solution (whether it includes a non-prescription medicine or only advice) or to refer to another healthcare professional (e.g. a medical doctor) to have an in-depth investigation and diagnosis. This assessment of patients' needs is a professional cognitive service, where pharmacists' professional skills are fully employed.

Pharmaceutical triage is facilitated by the accessibility of pharmacies. Pharmacies have long opening hours (including in many countries, during the night and at weekends). Furthermore, they have often a good geographic distribution. A recent FIP report revealed that governments have developed specific policies to ensure a fair distribution of pharmacies based on demographic criteria (18 countries; 25% of the countries studied) or geographic criteria (25 countries; 35% of the countries).⁽⁵⁾

Pharmacists are also often seen as among the most trusted professionals, which makes pharmacies premium local and community-based healthcare hubs for patients. Given all these points, it is easy to see why patients would choose to start their health journeys at pharmacy and, therefore, why we should facilitate this by making clear a compelling value proposition.

VALUE PROPOSITION OF PHARMACISTS

The pharmacy profession has both the ability and willingness to integrate self-care into health systems. Industry has invested in developing and demonstrating the value of its non-prescription medicines, in terms of health (and economic) outcomes, but often patients do not benefit fully primarily because of non-responsible use of them.

In most countries in the world, non-prescription medicines are not (fully) covered by health insurance — patients pay for such treatments out of their own pockets. When access to non-prescription medicines is associated with services to ensure the optimal treatment outcomes, it is a guarantee for the patients that their personal investment is more likely to result in improving (or maintaining) their health status.

But the involvement of pharmacists in self-care is also beneficial to the healthcare system, in terms of cost saving, efficiency and better access to care for more serious cases, whether or not the healthcare system suffers from medical doctors shortages. These benefits for healthcare sector are becoming more and more appreciated by governments and stake holders.

In England, the National Health System (NHS) has organised campaigns under the motto “think pharmacy first” in order to encourage patients to go to their local community pharmacists before they consider a visit to a medical doctors or the emergency room.

In Scotland, the NHS has, run for many years, its “Minor Ailments Scheme” through community pharmacies. This programme targets the most vulnerable Scottish patients who meet certain criteria (including annual income). In total, 900,000 Scottish patients (out of 5.3 million) have registered for this programme, which allows them to have their non-

prescription medicines reimbursed by NHS. Dispensing of such medicines is supported by clinical guidelines covering a wide array of minor ailments, including pain, lice, sore throat, conjunctivitis, colds, coughs and skin complaints, to list only a few. Pharmacists are compensated for this service through a capitation fee based on the number of patients registered in their pharmacies. This programme has resulted in 50,000 monthly visits to pharmacies and a decrease in the number of consultations with general practitioners.

Another interesting example comes from Switzerland. The national association of pharmacists has developed netCare, a programme focusing on common minor ailments. Twenty-four decision trees have been developed jointly by pharmacists and medical doctors. Based on these, pharmacists can offer lifestyle advice, deliver non-prescription medicines (which will eventually be covered by the health insurance) or offer a video conference linking the patient to a medical doctor in a telemedicine centre for a deeper investigation when needed. (A prescription can then be established by this medical doctor and faxed to the pharmacy.) In 73% of cases, pharmacists have been able to offer a solution by themselves, and in 20%, a video-conference was sufficient to solve the problem. Only 7% of patients needed a referral for a face-to-face interaction with a doctor (or an emergency unit visit). The intervention by pharmacists does not stop at dispensing. 3 days later, the patient is telephoned to ensure that his or her health problem has been solved. Pharmacists are paid 15 Swiss francs for the cognitive service provided based on the decision while there is a 48 Swiss francs charge for a video consultation with a doctor.

Other countries have implemented other options aimed at formalising the cognitive service and leading to the recommendation of medicines to patients. For example, in Brazil, the pharmacists' regulator (Conselho Federal de Farmácia) has adopted a regulation requiring pharmacists to formalise their selection of medicines through the establishment of a "pharmaceutical prescription". Such option aims to increase the accountability of the profession by ensuring that such recommendations are validated by a pharmacist; but patients may also better appreciate pharmacist's role of selection of medicines thanks to this formalisation.

There are now a number of good examples of pharmacists' value in supporting responsible self-care.

APPLICATION AND VARIABILITY

All the examples given above should be considered in their respective national context because there is high level of variation on how non-prescription medicines can be accessed in different countries. As revealed in a recent FIP report,⁽⁵⁾ non-prescription medicines can only be accessed through community pharmacies in 20 countries (out of 71 countries studied) and in another 23 countries, some non-prescription medicines can be sold outside pharmacies, while some can only be obtained in pharmacy.

The legal framework of non-prescription medicines stipulates the environment of operation of community pharmacy, but there are also variations between patients (across countries and within a country). Within the population

of a country, societal and cultural expectations around non-prescription medicines differ from one patient to another as guided by many factors. One of the most important factors is health literacy. One challenge to medicines regulators considering shifting a medicine's availability from pharmacy-only to over the counter and to be available in non-healthcare settings is how to assess this impact when dealing with literacy diversity, which may result in non-responsible use of medicines (including abuse). Even in developed countries like the USA, it is estimated that 36% of the population has limited health literacy.⁽⁶⁾ This population may not be aware of their literacy challenges and surely need an active intervention of pharmacist. The opportunity of such a systematic intervention is also influenced by the legal framework around the distribution of non-prescription medicines. Moreover, the intermediate and proficient health literacy level for the 64% remaining patients may not be sufficient. Sweden offers a recent example. In 2009, the Swedish government authorised the sale of paracetamol in supermarkets, but reversed this decision in 2015. This medicine can now only be sold in community pharmacies following Swedish Poisons Information Centre's reporting of a spike in cases of accidental poisoning and overdoses involving paracetamol.

CONCLUSIONS

The pharmacy profession is in a good position to shift its proposition value for non-prescription medicines into a health offer fully integrated within the healthcare system. To support such a shift, it is crucial that our profession not only documents the dispensing of non-prescription medicines, but also the associated services they deliver. Adjustments of the legal and economic framework will be needed, but there is growing evidence and experience to support such a change.

Author's background

BESANÇON, Luc is the General Secretary and CEO of the International Pharmaceutical Federation (FIP), which is a non-governmental organisation representing for over three million pharmacists and pharmaceutical scientists around the world. His email address is: generalsecretary@fip.org

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Pharmacological Treatment of Neuropathic Pain

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ABSTRACT

Neuropathic pain is a debilitating condition affecting a growing number of people around the world. It is notoriously difficult to manage and many patients are refractory to traditional analgesics. It is a clinical symptom reflecting an underlying condition that causes neuronal damage. Neuropathic pain can be classified according to the cause and origin of lesion or damage. Despite differences in cause and origin, symptoms are remarkably similar, pointing to the fact that the condition arises from a similar set of pathophysiological pathways. Adjuvants that target these pathological changes have now become the mainstay of treatment. Different guidelines exist with regard to their use. This review will provide an overview of the background of neuropathic pain and outline the commonly used pharmacological agents discussed in these guidelines.

Keywords: Neuropathic pain, Antidepressants, Antiepileptics, Opioids, Ketamine, Topical treatment

INTRODUCTION

As defined by the International Association for the Study of Pain (IASP), neuropathic pain is a direct result from a lesion or disease of the somatosensory system.^(1,2) Its prevalence is estimated to be ranging from 1.5% to 8% in the general population.^(3,4) Neuropathic pain is often challenging to manage. Not only does it impair one's functioning physically but also emotionally.⁽⁴⁾ Many of these patients develop concomitant morbidities such as sleep disturbances, anxiety, and depression, which are related to their pain syndromes.⁽⁴⁾ Potential burden on one's quality of life and economic costs to society could be huge.⁽⁴⁾ Therefore, optimal treatment is of utmost importance. This review will provide some background information regarding neuropathic pain and focus on its pharmacological treatments.

AETIOLOGY

The aetiology of neuropathic pain can be multifactorial. Any cause that can lead to neuronal damage or dysfunction contributes to its development (Table 1).⁽⁵⁾ The damage can be located in either the central nervous system or the peripheral nervous system and classified accordingly (Table 2).⁽²⁾ When

treating neuropathic pain, it is crucial to consider providing sufficient symptomatic relief, as well as tackling the underlying causes.⁽²⁾ In some cases (e.g. cancer), pain can have both nociceptive and neuropathic features and contribution from the nociceptive component should not be neglected.

Table 1. Causes of neuropathic pain⁽⁵⁾

Drug-induced/Toxin-induced	<ul style="list-style-type: none"> • Antimicrobials (e.g. isoniazid, ethambutol, nitrofurantoin, metronidazole) • Chemotherapeutics (e.g. cisplatin, oxaliplatin, thalidomide, vincristine) • Antiretrovirals (e.g. didanosine, ritonavir) • Ethanol • Heavy metals (e.g. arsenic, thallium)
Infection	<ul style="list-style-type: none"> • Herpes Zoster (Shingles) • HIV (HIV-related polyneuropathy)
Metabolic/Nutritional-related	<ul style="list-style-type: none"> • Diabetes Mellitus • Vitamin B₁, B₃, B₆, B₁₂ deficiency • Vitamin E deficiency
Mechanical	<ul style="list-style-type: none"> • Trauma • Nerve compression (e.g. by tumours) • Surgery (e.g. mastectomy, thoracotomy) • Amputation
Idiopathic	<ul style="list-style-type: none"> • Trigeminal neuralgia • Multiple sclerosis

Table 2. Neuropathic pain classification based on its location⁽²⁾

Location of injury	Disease
Central nervous system (Central neuropathic pain)	<ul style="list-style-type: none"> • Spinal cord injury • Spinal cord ischaemia • Cerebrovascular accident • Multiple sclerosis • Wallenberg's syndrome • Parkinson's disease
Peripheral nervous system (Peripheral neuropathic pain)	<ul style="list-style-type: none"> • Diabetic peripheral neuropathy • Trigeminal neuralgia • Post-herpetic neuralgia • Phantom limb pain • Lumbar and cervical radicular syndrome caused by nerve compression • Brachial plexus avulsion • Lumbosacral plexopathy • Alcoholic polyneuropathy

SYMPTOMS

Despite obvious differences in aetiology, neuropathic pain is characterised by a common set of symptoms.^(5,6) Symptoms can be either positive or negative.^(7,8) Positive symptoms are changes in sensation or increased sensation. These positive sensations consist of spontaneous (non-stimulus dependent) and evoked (stimulus-dependent) components.^(5,6) In the case of evoked pain, amplified pain in response to a usually painful stimulus (hyperalgesia) or pain in response to non-painful

stimuli (allodynia) such as light touch, brush, cold or heat can occur.^(5,6) Sometimes an abnormally painful reaction to a stimulus may happen (hyperpathia), and this pain may increase with prolonged stimulation. Pain may occur continuously or intermittently. Continuous neuropathic pain is often described as burning pain, while intermittent neuropathic pain is described to present as shooting, stabbing, or electric shock-like pain paroxysms.^(5,6) Abnormal sensations (paraesthesia) for example, 'pins and needles' and tingling, can also be present. Negative symptoms involve partial or complete sensory deficit in the painful areas, such as hypoaesthesia and hypoalgesia.^(5,7,8)

PATHOPHYSIOLOGY

Upon nerve injury, specific changes occur at the level of periphery and spinal cord.^(9,10) These pathophysiological changes manifest themselves as the characteristic symptoms of neuropathic pain. Pharmacological agents that target these changes could be potential treatments. Injured peripheral nociceptive afferent nerves re-grow to form newly grown nerves known as neuromas. These neuromas have increased quantity and density of sodium (Na⁺) channels. Consequently, action potentials generate and propagate more readily. In addition, neuromas may grow into nearby afferent neurones, forming atypical connections. Spontaneous discharges spread to these normal neurones and they become unstable and chaotic as well. Therefore, pain or abnormal sensations may originate from intact neurones that are affected by these neuromas. There is also evidence that nerve injury induces up-regulation of transient receptor potential vanilloid 1 (TRPV1) in peripheral endings of nociceptive C and A δ -fibres.⁽⁹⁾ TRPV1 proteins are transmembrane ion channels that are activated in response to noxious heat or high acidity.^(11,12) Up-regulation of such may induce heat hyperalgesia experienced by some patients. Activation of immune cells and heightened responsiveness to pro-inflammatory cytokines released from damaged cells may also be involved.⁽¹⁴⁾ In the central nervous system, large myelinated A β -fibres that normally signal harmless sensations such as light touch could be remodelled to produce nociceptive responses, resulting in allodynia.^(2,9,10) Other central mechanisms include up-regulation of calcium (Ca²⁺) channels, particularly those with the alpha-2-delta (α 2 δ) subunit. Down-regulation of inhibitory GABA-ergic neurones and loss of intrinsic opioid receptors, accompanied by a reduction in supraspinal descending inhibitory (serotonergic and noradrenergic) pathways, facilitate unopposed transmission of pain signals to the brain, leading to symptoms such as hyperalgesia.⁽¹³⁾ Phosphorylation and up-regulation of N-methyl-D-aspartate (NMDA) receptors may also play a role.⁽¹⁴⁾ Due to these multiple neuronal changes, following the apparent healing of damaged nervous structures, neuropathic pain may persist for years or be life-long. Prognosis hence tends to be poor.

PHARMACOLOGICAL MANAGEMENT

Pharmacological treatments target pathways that are altered by nerve damage. It is important to note that neuropathic pain is a clinical manifestation of an underlying pathological

process rather than a disease itself. Hence, to provide optimal management, underlying disease should be dealt with simultaneously.⁽²⁾ Such disease-modifying measure should be started as soon as possible to prevent chronification of neuropathic pain.⁽²⁾ Taking diabetic peripheral neuropathy (DPN) as an example, hyperglycaemia is the primary cause for nerve damage. Effective control of blood glucose level is the mainstay of therapy. Evidence also suggested that adherence to antidiabetics is associated with reduced diabetic foot pain.⁽¹⁵⁾ Another example is post-herpetic neuralgia (PHN). Early management of shingles by antivirals can actually reduce the risk and severity of PHN.⁽¹⁶⁾ Herpes Zoster vaccine can be used to prevent infection that would otherwise have occurred in the first place.⁽¹⁷⁾

The World Health Organisation (WHO) analgesic ladder (**Fig. 1**), which was originally developed to guide the treatment of cancer-related pain, can be adopted to provide a step-by-step approach to the management of neuropathic pain.⁽¹⁸⁾ In this case, the adjuvants are drugs that, by their actions on the neuronal pathways, reduce neuropathic pain. Different guidelines published by various international institutions are available to provide evidence-based treatment recommendations.⁽¹⁹⁻²¹⁾ These guidelines were developed based on scientific evidence of efficacy and safety, as well as clinical experience with the individual drugs. The recommendations for neuropathic pain treatment are generally similar.⁽²⁾ When applying these guidelines, it is important to note that although there are many types of central/peripheral neuropathic pain syndromes, most randomised controlled trials (RCTs) have only investigated the short-term drug effectiveness in PHN or DPN.⁽²²⁾ Relevance to other clinical conditions or to long-term use is currently unknown. Moreover, head-to-head trials comparing the efficacy and tolerability of different treatments are scarce.⁽²²⁾ Direct comparisons of these medications are hence difficult. Lastly, there is considerable heterogeneity among various syndromes.⁽²²⁾ Positive response in one condition does not always predict the same response in another condition.

Some of the more important drugs will be discussed below.

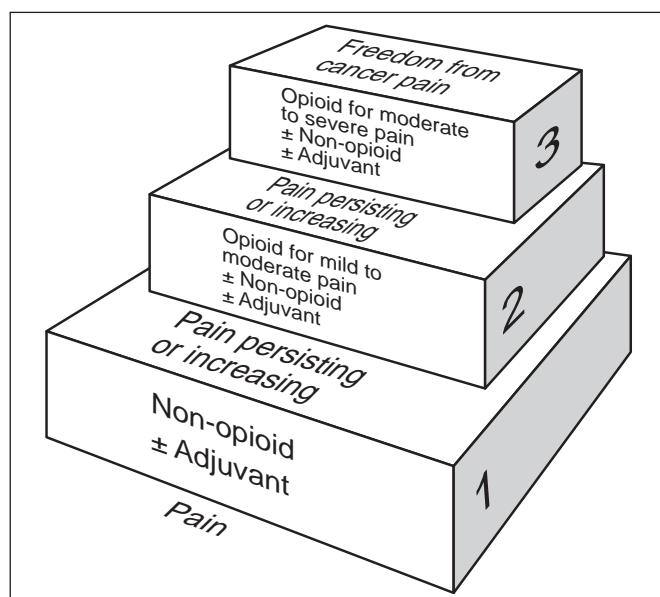


Figure 1. The WHO analgesic ladder[®]

Paracetamol & Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Traditional analgesics are often inadequate as monotherapy in neuropathic pain.⁽¹²⁾ However, they can still be of some use, particularly in situations where there is mixed pain. Most benefits were seen especially during the acute phase of PHN, DPN, and post-traumatic peripheral neuropathies.⁽²⁾ Paracetamol exhibits its analgesic effects via direct/indirect inhibition of central cyclo-oxygenases, and activation of the endocannabinoid system and spinal serotonergic pathways.^(24,25) As mentioned, neuronal inflammation may also be involved in the generation of neuropathic pain. Hence, NSAIDs, including COX-2 inhibitors, may well be effective as shown by animal models.⁽²⁶⁾ However, in clinical studies, they have demonstrated either some efficacy; no efficacy; or equivocal efficacy.^(2,27) They can be tried and stopped if there is no positive response.

Antidepressants

Tricyclic antidepressants (TCAs) and serotonin noradrenaline reuptake inhibitors (SNRIs) are useful in management of neuropathic pain. Both are inhibitors of serotonin and noradrenaline reuptake.⁽²⁸⁾ They are particularly effective for the continuous, burning type of pain.⁽²¹⁾ It is interesting to note that selective serotonin reuptake inhibitors (SSRIs) have only demonstrated weak analgesic properties and their clinical relevance is controversial.^(15,16) This phenomenon could suggest that the noradrenergic pathway may at least play a specific role in neuropathic pain.^(29,30)

Tricyclic antidepressants (TCAs)

TCAs augment the descending serotonergic and noradrenergic inhibitory pathways, thereby attenuating pain transmission through the spinal cord.^(13,28) Other plausible mechanisms have been proposed, including the modulation of peripheral neuronal Na⁺ channels.^(6,13) The efficacy of TCAs is mainly established in DPN and PHN.⁽⁶⁾ Their analgesic effect is independent of their antidepressant activity as pain relief is evident at lower doses (100 mg) than those used for depression (300 mg).⁽²⁾ The onset of action is also quicker (within 1 to 7 days) after treatment initiation compared with that for the treatment of depression.⁽²⁾ Amitriptyline and nortriptyline are commonly used in clinical practice, though other TCAs are used occasionally. TCAs are inexpensive and they can be given as once-daily dosing regimen, which greatly enhances compliance. Sedation (H₁-receptor blockade), orthostatic hypotension (α_1 -adrenoceptor blockade), and anticholinergic adverse effects (muscarinic receptor blockade), such as dry mouth, urinary retention, and constipation, can be quite troublesome.⁽³¹⁾ These side effects can be minimised by administering the drug at night, using a low starting dose, and by slow titration.⁽²²⁾ Switching to a secondary-amine TCA (e.g. nortriptyline, desipramine) can also be considered as they are associated with a lower risk of these adverse effects.^(6,22) In terms of amitriptyline, the initial dose for the elderly aged

greater than 60 years old would be 5 to 10 mg at night. Higher initial dose (25 mg) can be used for younger individuals.^(21,32) The usual daily maximum would be 150 mg.^(21,32)

Serotonin noradrenaline reuptake inhibitors (SNRIs)

SNRIs act similarly as the TCAs on the serotonergic and noradrenergic pathways.⁽²⁸⁾ Duloxetine and venlafaxine are the main SNRIs in use and their efficacy is mainly established in DPN.^(6,28) Side effects such as dry mouth, sweating, and sexual dysfunction have been reported.⁽²⁵⁾ The efficacy of duloxetine in painful DPN is well documented with FDA approval.⁽²⁾ Its dosing is simple, normally as 60mg daily to 120 mg daily in one or two doses.^(21,22) Nausea seems to be the most common side effect, which has resulted in discontinuation rates of approximately 15% to 20% across studies.⁽⁶⁾ It can be reduced by initiating the drug at 30mg once daily for the first week before titrating to 60mg once daily.⁽²²⁾ Unlike venlafaxine, it is seldom associated with electrocardiographic abnormalities or blood pressure changes.⁽²⁵⁾ Venlafaxine (as controlled-release preparation) can be started at 37.5 mg daily, tapering up to 150-225 mg daily as required.^(21,22,25) Its main drawbacks are elevated arterial pressure and cardiac conduction abnormalities, which have been reported in 5% of patients with DPN treated with venlafaxine.^(6,25) As the SNRIs have fewer receptor interactions, they may be preferable to the TCAs.

Antiepileptics

Antiepileptics are effective for those types of pain that are described predominantly as shooting, stabbing, electric shock-like, or 'pins and needles'.⁽²¹⁾ Those that are relevant to neuropathic pain treatment include the alpha-2-delta ($\alpha_2\delta$) ligands (gabapentin & pregabalin) and carbamazepine (and its related analogue oxcarbazepine). Other antiepileptics, for instance, sodium valproate and topiramate, are sometimes used. However, the evidence to support their use is not robust.⁽²⁾ Additionally, they have high potential for adverse effects. Thus, they are generally recommended only when the other more effective medications have failed or are not tolerated. With regard to dosing, it is generally similar to that of the management of epilepsy.⁽³³⁾

Alpha-2-delta ($\alpha_2\delta$) ligands

Gabapentin and pregabalin reduce pain by modulating signal transduction mediated by calcium (Ca²⁺) channels. They are Ca²⁺ channel $\alpha_2\delta$ ligands, which bind to the $\alpha_2\delta$ -1 subunits and inhibit the nerve injury-induced trafficking of the α_1 pore forming units of Ca²⁺ channels from cytoplasm to plasma membrane of presynaptic terminals of dorsal horn neurones.^(34,35) The resulting reduction in Ca²⁺ influx decreases excitatory neurotransmitter release (e.g. glutamate) and pain signal transmission. Their efficacy is mainly established in PHN and DPN, though in other neuropathic pain syndromes (phantom pain, complex regional pain syndrome type I [CRPS-1], and central neuropathic pain due to spinal cord injury), their efficacy has also been reported.^(2,6) They are normally started at low

doses and titrated cautiously to minimise adverse effects. Apart from their main adverse effects of dizziness, somnolence, peripheral oedema and weight gain, they are generally well tolerated.⁽²⁵⁾ There is no known hepatic enzyme-mediated drug-drug interaction. The initial dosage for gabapentin would be 100 mg three times daily, increasing to the usual maintenance dose of 300 mg three times daily. The maximum daily dose would be 3600 mg.^(21,25) For pregabalin, it is usually started at 75mg twice daily, which can be increased to the usual maintenance dose of 150 mg twice daily. The maximum dose would be 300 mg twice daily. Dosage reduction is warranted in renal impairment.^(21,25)

The major difference between them is their respective pharmacokinetic profiles. The pharmacokinetic profile of pregabalin is linear which means that its dosing is simpler and more straightforward.⁽²²⁾ The titration period is shorter and upward titration by 75 mg can be done every 3 days. By contrast, gabapentin has non-linear pharmacokinetics. Dosage increase should be gradual with small increment of dose each time.⁽²²⁾ It can take up to 2 months for titration to the full dosage. Therefore, pregabalin may be more suitable for those who require quicker pain relief. Other advantages of pregabalin include its twice-daily administration regimen and its narrower dosage range.⁽²²⁾

Carbamazepine & Oxcarbazepine

Carbamazepine has been extensively studied in the treatment of trigeminal neuralgia for which it remains particularly effective. Approximately 70 to 80% of patients experience a reduction of pain within 48 hours.⁽³⁶⁾ Carbamazepine is a use-dependent blocker of neuronal Na⁺ channels. It preferentially binds to the closed Na⁺ channels in their inactivated state, preventing them from returning to the resting state. In the presence of ectopic discharge activity, as in neuropathic pain, there is a high proportion of channels in their inactivated state which are susceptible to blockade by carbamazepine.⁽³¹⁾ Lancing pain in trigeminal neuralgia is probably mediated by this excess of Na⁺ channel activity.⁽¹⁰⁾

While it is recommended as the first-line agent in idiopathic trigeminal neuralgia, its use in other types of neuropathic pain syndrome is not as evident.⁽²²⁾ Aside from that, carbamazepine has many demerits which make it a less desirable treatment option.⁽²⁾ First of all, it has a narrow therapeutic range. Together with its ability to autoinduce its own metabolism, optimal dosing becomes extremely difficult.⁽²⁵⁾ Dosage has to be titrated slowly and carefully, in order to account for autoinduction. Secondly, it has high potential for many cytochrome p450 mediated interactions.⁽²⁵⁾ Thirdly, it is associated with a wide range of gastrointestinal, neurological, and dermatological adverse effects (e.g. nausea, drowsiness, dizziness, ataxia, diplopia, etc.). Severe skin reactions (e.g. Stevens-Johnson Syndrome) are of particular concern in individuals with the HLA-B*1502 allele (high prevalence in Han Chinese).⁽²⁵⁾ Around 19% of patients are unable to tolerate carbamazepine.⁽³⁶⁾ Controlled-release is usually used to reduce the peak concentration-

related side effects. Initially, dose should be 100 mg twice daily and increased as tolerated according to response up to a maximum of 600 mg twice daily. Once the condition has been stabilised for several weeks, the dose can be reduced to the minimum required for adequate pain control.^(21,25)

Oxcarbazepine is an analogue of carbamazepine. It can be worth trying for patients who cannot tolerate carbamazepine, or in whom carbamazepine is not effective. Compared with carbamazepine, oxcarbazepine may have fewer neurological side effects and drug interactions.⁽²⁵⁾ Up to 66% of patients who did not respond to carbamazepine have shown positive result with oxcarbazepine.⁽³⁷⁾ The commencing dose would be 150 mg twice daily. Usual maintenance dose is 300 to 600 mg twice daily up to a maximum of 900mg twice daily.⁽²¹⁾

Opioids

Opioids exert their analgesic effects mainly via activation of opioid mu (μ) receptors at peripheral tissues, dorsal horn, and supraspinal sites.⁽³¹⁾ The end results are inhibition of excitation of peripheral nociceptive nerve terminals, and inhibition of pain impulse transmission through the spinal cord.⁽³¹⁾ They are not considered to be the first-line treatment due to concerns for their unfavourable long-term safety profile (immunological changes, hypogonadism, physical and psychological dependence) and the possible development of opioid-induced hyperalgesia, which has occurred in animal models.^(6,22) However, they have a rapid onset of action and are effective for nociceptive pain. Consequently, opioids are generally reserved as second-line agents among all current recommendations, except in situations such as during acute phase of neuropathic pain, cancer pain, episodic exacerbations of neuropathic pain, as well as during the titration with the other more useful medications when opioids are prescribed as an add-on therapy.⁽²²⁾ They could also be alternatives for those who do not show successful response to antidepressants and/or antiepileptics. Higher doses are usually required for the treatment of neuropathic pain compared with that for nociceptive pain.⁽⁶⁾ The corresponding adverse effects will therefore be more severe.

Morphine and oxycodone are strong μ -receptor agonists and they have been proven to be efficacious in PHN and DPN in several RCTs.⁽⁶⁾ There is no standard dosing since dosage requirement varies substantially from patient to patient.⁽²⁾ Doses should be individualised to provide adequate pain control while minimizing adverse effects.^(21,25) Dosage adjustment in renal impairment is required.⁽²⁵⁾ Constipation, sedation, nausea and vomiting are the most common side effects.⁽²⁵⁾ Nausea and vomiting may occur initially, which subside with continued administration. Using low initial doses and giving prophylactic antiemetic drugs can reduce the risk.⁽²⁵⁾ However, little, if not none, tolerance develops towards constipation. Close monitoring of patient's bowel function and attention to lifestyle factors should be considered.^(22,25) Regular laxative use is essential as soon as chronic opioid therapy is initiated.⁽²⁵⁾ Another problem is that they should be used very cautiously in people with history of drug abuse.^(22,25)

Tramadol is a weak opioid μ -receptor agonist. It also inhibits the reuptake of serotonin and noradrenaline.⁽²²⁾ Its efficacy is predominantly established in DPN.⁽⁶⁾ The risk of abuse and other opioid-related adverse effects is lower. The major drawbacks of tramadol are its potentials to lower seizure threshold and to induce serotonin syndrome.^(22,25) The starting dose of tramadol should be 50 mg once or twice daily, increasing to a maximum daily dose of 400mg in patients younger than 75 years of age, or 300mg in those 75 years or older.^(21,25) Dosage should be reduced in individuals with renal and/or hepatic impairment to avoid drug accumulation.^(22,25)

Tapentadol is a new opioid analgesic that acts via a dual mechanism of action. It is different from the classical opioids in that apart from its agonistic activity on opioid μ -receptors, it also inhibits noradrenaline reuptake.⁽³⁸⁾ Affinity of tapentadol to μ -receptor is much lower (20 times less) than that of morphine. However, its analgesic potency is only about 3 times less than that of morphine.⁽³⁸⁾ Such discrepancy could be explained by its activity on noradrenaline reuptake which strengthens the descending inhibition of pain impulse transmission through the dorsal horn of the spinal cord. This synergism has been effective in the treatment of neuropathic pain as the drug has demonstrated comparable efficacy with other strong opioids (e.g. oxycodone) but greater tolerability.^(28,39) Another advantage is that its abuse potential seems to be small, similar to that of tramadol.⁽²⁸⁾ Unlike tramadol, there is no concern for serotonin toxicity due to its minimal serotonergic effects.⁽²⁸⁾

Other opioids such as fentanyl and methadone have also been used with some success in patients with neuropathic pain. Methadone differentiates itself from other opioids in that it has NMDA receptor antagonistic activity, which might provide additional benefits.⁽²⁾ It has exhibited some efficacy in various RCTs.⁽⁶⁾ Yet, its potential to prolong QT interval and its long half-life make it a less preferable choice.⁽²⁵⁾ Fentanyl has the advantage of being suitable to use in renal impairment as there is no significant accumulation of active or toxic metabolites.⁽²⁵⁾ Buprenorphine has also been suggested to offer some advantages for treating severe neuropathic pain in the elderly.⁽²⁾

N-methyl-D-aspartate (NMDA) receptor antagonists

NMDA receptors are excitatory glutamatergic receptors involved in the afferent transmission of nociceptive signals at the spinal level. Repetitive firing from nociceptive neurones (as occurring in neuropathic pain) can actually facilitate pain transmission at the dorsal horn synapses by activation and up-regulation of NMDA receptors.⁽¹⁴⁾ The end result is enhanced and amplified trafficking of pain signals to the brain.⁽¹⁴⁾ Blocking of these receptors by NMDA receptor antagonists could be an effective alternative to existing treatments. Other mechanisms of NMDA receptor antagonists include the enhancement of descending inhibition and anti-inflammatory effects.⁽¹⁴⁾ NMDA receptors also play a role in the development of tolerance to

opioids. Thus, NMDA receptor antagonists may enhance the opioid analgesic effectiveness by preventing the development of opioid tolerance.⁽¹⁴⁾

Ketamine is a NMDA receptor antagonist used intravenously at sub-anaesthetic doses to treat various neuropathic pain syndromes (e.g. CRPS-1, PHN, phantom limb pain).^(14,28) There is no consensus on the administration protocol. The duration of analgesia is determined by the time of infusion. Short-term infusions produce potent analgesia only during administration whereas prolonged infusions for 4 to 14 days display long-term analgesic effects for up to 3 months.⁽¹⁴⁾ Repeated administrations at regular intervals are thus required. One of the main problems with ketamine is the induction of a psychedelic state (e.g. agitation, hallucinations, amnesia) and cardiovascular stimulation.⁽¹⁴⁾ These side effects can be minimised by pre-treatment with benzodiazepines and α_2 -adrenoceptor agonists (clonidine).⁽¹⁴⁾ Another means is to administer the drug intrathecally. Intrathecal administration allows the drug to be delivered directly to the central receptors. Dosage requirement is smaller compared to systemic administration and adverse effects are therefore reduced.⁽¹³⁾ Its prolonged use could cause organ damage and dependence, as shown in recreational users.⁽¹⁴⁾ Because of such uncertainty on the long-term safety profile of ketamine, it is restricted to refractory cases who have failed to respond to other agents. Other dosage forms of ketamine are also available. Topical ketamine, either alone or in combination with other analgesic agents, has also been shown to be effective in chemotherapy-induced neuropathic pain and radiation-induced neuropathic pain.⁽²⁾

Other oral NMDA receptor antagonists (e.g. dextromethorphan, amantadine, memantine) have only demonstrated limited analgesic potential.⁽²⁾ There are occasional reports of using dextromethorphan in the treatment of refractory neuropathic pain. High-dose dextromethorphan (400mg) has been found to be effective for painful polyneuropathy but ineffective for PHN.⁽⁴⁰⁾

Topical treatments

Two locally acting topical preparations - lignocaine and capsaicin, for neuropathic pain will be discussed herein. Since they act at peripheral level, they are most effective when the pain is localised, originating from peripheral sources (e.g. PHN & DPN), or from a central source that induces peripheral nerve dysfunction.⁽¹³⁾ Local action has the advantages of being less likely to cause systemic adverse effects due to limited absorption and of producing higher local drug concentration due to direct application to the area of pain.

Increased expression of neuronal Na⁺ channel is evident in neuropathic pain, causing spontaneous ectopic discharges. Lignocaine is a local anaesthetic that can stabilise these ectopic discharges by causing reversible block of Na⁺ channels along peripheral nerve fibres.⁽³¹⁾ It is effective for well-localised

neuropathic pain. Topical 5% lignocaine patch has displayed excellent efficacy in multiple RCTs involving patients with PHN or allodynia caused by other neurological conditions.^(6,22) Up to three patches can be used at the same time for up to 12 hours in a 24-hour period.⁽⁶⁾ Adverse effects may include skin irritation (redness/swelling) and abnormal skin sensations.⁽²²⁾ Long-term use is often limited due to the possible development of skin hypersensitivity.⁽²²⁾

Capsaicin is a pharmacologically active agent derived from chili peppers.^(11,12) It is a potent and highly selective agonist of the TRPV1 protein, a transmembrane cation channel with high permeability to Ca²⁺.⁽¹²⁾ TRPV1 is expressed in nociceptive sensory nerves and binding of capsaicin initiates influx of Ca²⁺ and propagation of action potentials.^(11,12) This results in a painful sensation. Capsaicin is chemically stable and can cause prolonged activation of TRPV1. Persistent opening of TRPV1 channels allows massive influx of Ca²⁺.⁽¹²⁾ TRPV1 expressed in intracellular organelles can also be activated by capsaicin, providing another source of Ca²⁺. The resulting enormous intracellular Ca²⁺ signal overwhelms the local Ca²⁺ homeostatic mechanisms.⁽¹²⁾ Ca²⁺ overload could induce protease activation and cytoskeletal depolymerisation. An additional effect of high capsaicin concentrations is the direct inhibition of mitochondrial function.⁽¹²⁾ Fast axonal transport is interrupted and the nociceptive fibres are said to be defunctionalised.⁽¹²⁾

Capsaicin cream (0.075%) and capsaicin patch (8%) are the two topical capsaicin applications currently available. The lower concentration capsaicin cream is less effective and at best is only moderately effective in PHN.⁽²¹⁾ It requires multiple applications per day and continuous application to be effective. The higher concentration preparation is more effective. It has demonstrated effectiveness in PHN and HIV neuropathy.⁽²⁾ Compared to the 0.075% capsaicin cream, it has the advantage of requiring less frequent application. A single 60-minute application with maximum of four patches at a time can provide effective pain relief for up to 12 weeks.^(6,22) However, initial pain associated with its application can be excruciating and may necessitate prior lignocaine application and opioid pre-medication.⁽⁶⁾ Another detrimental factor is its high cost.⁽²⁾ Long-term safety is questionable but it seems to be safe as standard sensory evaluation in PHN and HIV neuropathy after repeated uses for up to 1 year did not show any sensory impairment.⁽⁶⁾

DISCUSSION: MULTIMODAL THERAPY & TREATMENT OF COMORBIDITIES

Multiple mechanisms are involved in the development of neuropathic pain. Therefore, combining drugs with different pharmacological actions could theoretically maximise analgesic efficacy while allowing lower doses of each individual drug to minimise toxicities. While this multimodal approach seems to be quite intuitive, there is already primitive

evidence from several placebo-controlled trials to support its advantages. In patients with PHN or DPN, better efficacy has been confirmed with gabapentin plus either nortriptyline or morphine compared to gabapentin monotherapy without a significant increase in adverse effects.^(41,42) Similarly, gabapentin combined with oxycodone has been shown to be more effective than gabapentin alone in patients with DPN.⁽⁴³⁾ Although combination therapies seem to produce promising treatment outcomes, they are not without problems. Some medications should be combined cautiously due to their additive toxicities. Serotonin syndrome, though relatively uncommon in clinical practice, should not be overlooked when initiating combination therapy of tramadol and TCAs/SNRIs.⁽²²⁾ Combination of pro-arrhythmic agents such as TCAs and methadone can increase the risk of QT prolongation.⁽²⁵⁾ Most of these medications can induce CNS disturbances and impair psychomotor performance. Effects may be more pronounced when they are used concomitantly.⁽²¹⁾ Carbamazepine may reduce analgesic effects of other agents by inducing their metabolism.⁽²⁵⁾

To make an appropriate choice of agent for treatment of neuropathic pain, prescriber should consider other comorbidities. Sleep disturbances, depression and anxiety are common comorbidities of neuropathic pain. Poor pain control could give rise to insomnia. Drugs with sedative property are useful in this case. Anticipation of pain when pain is poorly controlled may lead to feelings of anxiety. Gabapentin and pregabalin are preferred because of their anxiolytic effect.⁽⁶⁾ As high as 70% of neuropathic pain patients will have primary or secondary depression related to their pain syndromes.⁽⁴⁴⁾ Antidepressants can thus be quite beneficial.

CONCLUSION

By and large, specific first-line pharmacological agents for neuropathic pain encompass antidepressants and antiepileptics. Opioids are used as second-line in most of the cases. Topical agents and ketamine can be tried as alternatives to the above treatments. Until more evidence from direct head-to-head studies become available, treatment will still be based on a trial-and-error approach. Prescribers should make their choice of treatment based on the severity of the neuropathic pain syndrome, adverse effect profile and cost-effectiveness of the medications, presence of comorbidities, renal/hepatic impairment and drug-drug interactions. Therapeutic regimen of each patient should be individually tailored to maximise benefits while minimising the negative impact to quality of life.

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.pccch.com) to fill in their answers there.)

1. With regard to antidepressants, which of the following statements is incorrect?

- A. Common side effects of TCAs include sedation, orthostatic hypotension, and anticholinergic effects
- B. SSRIs are effective for the treatment of neuropathic pain
- C. Duloxetine is FDA approved for the treatment of DPN
- D. Doses of TCAs used for the treatment of neuropathic pain are lower than that for depression

2. Which of the following statements is correct for antiepileptics?

- A. Carbamazepine is effective for all types of neuropathic pain
- B. Pregabalin has the same pharmacokinetic profile as gabapentin
- C. Severe skin reactions of carbamazepine are of particular concern especially in patients with the HLA-B*1502 allele
- D. Pregabalin and gabapentin are prone to a wide range of hepatic enzyme-mediated drug-drug interactions

3. With regard to ketamine, which of the following is/are correct?

- A. It is a NMDA receptor antagonist
- B. It can induce a psychedelic state
- C. It can be administered intrathecally
- D. All of the above

4. Which one of the following statements correctly describes neuropathic pain?

- A. Neuropathic pain only involves peripheral nerves
- B. It is sufficient just to provide symptomatic treatment irrespective of the underlying cause
- C. Pathophysiological changes in neuropathic pain include alterations in ion channel expression and abnormal neuronal growths
- D. Post-herpetic neuralgia is a type of central neuropathic pain

5. With regard to opioids, which of the following statements is/are correct?

- A. The maximum daily dose of tramadol for patients aged 75 years or above is 400mg
- B. Tapentadol selectively inhibits the reuptake of serotonin
- C. Opioids are generally used as first-line agents for neuropathic pain
- D. None of the above



2 CE Units
**Pharmacological Treatment
of Neuropathic Pain**

6. Topical agents are used for the treatment of neuropathic pain. Which of the following statements is/are correct in this regard?

- I. Lignocaine 5% patch is applied once daily over 24 hours
- II. Capsaicin exerts its analgesic activity by selectively blocking the TRPV1 transmembrane cation channel
- III. Topically applied ketamine has shown efficacy in chemotherapy-induced neuropathic pain
- IV. Capsaicin 8% patch is effective for up to 12 weeks after patch removal

- A. I only
- B. I and III
- C. II and IV
- D. III and IV

7. What is the most significant concern of using tramadol and amitriptyline concurrently?

- A. They can both cause sedation
- B. Pro-arrhythmic activity of amitriptyline can be potentiated by tramadol
- C. Additive serotonin toxicity
- D. None of the above

8. With respect to pharmacological management of neuropathic pain, which of the following statements is correct?

- A. Paracetamol and NSAIDs should never be used as they are ineffective for neuropathic pain
- B. Opioids are fast acting and effective for acute phase of neuropathic pain
- C. Many head-to-head trials are available for comparing efficacy and tolerability of different therapeutic agents
- D. WHO analgesic ladder should only be reversed for neuropathic pain that is cancer-related

9. Which of the following situations correctly describe(s) the management approach of neuropathic pain?

- A. Reviewing antidiabetic treatment in a patient with diabetic peripheral neuropathy
- B. Modifying vincristine dose of a patient suffering from vincristine-induced neuropathy
- C. Prescribing antivirals for an elderly with early shingles
- D. All of the above

10. Which of the following pharmacological agent is the most suitable choice for a patient suffering from neuropathic pain associated with anxiety and sleep disturbance?

- A. Naproxen
- B. Oxycodone
- C. Pregabalin
- D. Ketamine

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 224(D&T)

Biosimilar Pharmaceutical Products of Recombinant Human Growth Hormone (rhGH) Currently Available on Market

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

Pharmaceutical Society of Hong Kong - Updates on PSHK Student Chapter

The Pharmaceutical Society of Hong Kong (PSHK) Student Chapter consists of pharmacy students from both **The University of Hong Kong (HKU)** and **The Chinese University of Hong Kong (CUHK)**. The Student Chapter intends to extend the missions of PSHK in promoting the pharmacy profession, enhancing the reputation of the pharmaceutical society, and contributing to the public health and welfare. In addition, the Student Chapter serves as a great platform for student members to share their concerns and run programs for students and other members of the community with an interest in pharmacy practice.

After a very successful PHAR-YES (Pharmacy Youth Education Scheme) programme in 2015, chiefly organized by the key student chapter coordinators from CUHK and HKU, PSHK Student Chapter decided to continue to run this meaningful event to enlighten our secondary school students on their knowledge of pharmacy, providing them with more guidance on the pharmacy profession as well as educating them the importance of the 'Quality Use of Medicines'. The program targets Form 4 or above secondary students, aiming to offer them more background information of pharmacy as a university subject. The program consists of various educational events and games that will be operated over 2 days. This year we are most delighted to host the event in the CUHK campus, where the first Bachelor of Pharmacy program was started, and with the support of both CUHK and HKU pharmacy faculties, we will surely have a very successful programme just like last year!

Another very exciting initiative of the Student Chapter this year is the *2016 PSHK Young Pharmacists & Student Chapter mentorship programme*. It is a one-year programme which starts from April 2016 to March 2017 where pharmacists from various sectors are invited to be mentors to some 3rd year pharmacy students from both CUHK and HKU pharmacy faculty. Through this program, we hope to pass on our

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experience and legacy to our fellow students and be able to support them in better understanding the pharmacy profession, as they will definitely be the pillars for a more cohesive pharmacist community in Hong Kong.

Summary Report on the Hong Kong Pharmacy Conference (February 27-28, 2016)

On February 27-28, 2016, 665 delegates from 6 countries gathered in the Hong Kong Convention and Exhibition Center (HKCEC) for the 2016 Hong Kong Pharmacy Conference. Led by the School of Pharmacy of the Chinese University of Hong Kong, this was the best attended Pharmacy Conference in recent history. It was a successful local thematic conference that met international standards.

There are seven co-organizers for the annual Hong Kong Pharmacy Conference. They are: The Pharmaceutical Society

of Hong Kong, The Practising Pharmacists Association of Hong Kong, The Society of Hospital Pharmacists of Hong Kong, The Department of Pharmacology and Pharmacy of the University of Hong Kong, School of Pharmacy of The Chinese University of Hong Kong, Department of Health and Hospital Authority. The co-organizers each takes turn to host the annual conference to meet three key objectives:

- To review the latest breakthroughs in drug therapy and the recent trend in disease management;

- To alert the pharmacy community of emerging transformative innovations in patient care enabled by scientific and technological advances, changes in demographics and healthcare financing, and government policy; and
- To facilitate networking by the conference delegates across disciplinary, institutional, and geographical boundaries.

The theme of the 2016 conference was “**The Art and Science of Integrated Pharmacy Practice.**” This was a bold departure from the themes of previous conferences, which essentially were creative interpretations of the art of pharmacy practice. The 2016 Pharmacy Conference had two main goals: (1) to reconnect with the scientific roots of pharmacy practice and (2) to imagine how advances in science and technology could be harnessed to elevate the standard of practice characteristic of an advanced economy.

The completion of the human genome project in April 2003 ushered in a decade of spectacular advances in life sciences at breakneck pace. This resulted in enhanced understanding of the complexity of disease, as indicated by the 5-fold increase in the International Classification of Disease from 14,000 to 70,000 effective on October 1, 2015. Moreover, the life science revolution dramatically expanded the therapeutic arsenal for tackling heretofore recalcitrant diseases like cancer, hepatitis, hypercholesterolemia, and advanced Parkinson’s disease. All except hepatitis was discussed at this conference.

Aside from the therapeutic triumphs just mentioned, the Conference also featured game-changing scientific and technological advances like gene sequencing and editing, nanotechnology, biosimilar, wearables, internet of things, and Big Data. By engaging the patient in monitoring the progress of drug therapy and in reporting the occurrence of adverse drug effects real time, the stage is set for precision medicine, a translational research priority mentioned prominently by President Barack Obama in his 2015 State of the Union Address. 3D printing of tablets is an emerging enabling technology that has attracted considerable attention of late, particularly after the methodology has gained regulatory approval in the United States in August 2015. Professor Simon Gaisford of the UCL School of Pharmacy in the United Kingdom shared the highlights of his pioneering research and invaluable insight in the niche of 3D printing in pharmaceutical manufacturing.

Against the historical average of 28 drugs approved per year in the current decade, the high of 45 drugs approved in 2015 by the FDA is a remarkable scientific as well as regulatory achievement. Nevertheless, the huge price tag of many of these drugs may deny the very patients who will benefit from such innovative, life-saving medicine. This paradox has ramifications in the business model of drug discovery, development, regulation and use. Professor Stuart Schweitzer, a world renowned health economist at UCLA, did not think that escalating research costs were the driver of drug prices. He went on to suggest that value-based pricing could be a solution to this drug access dilemma. On the positive side, the substantial public outcry of exorbitant prices of specialty drugs may be a window of opportunity for pharmacists to be innovative and entrepreneurial in sharpening their art of caring for their better-informed patients. By mandating patient-centred services that are not possible in the present Hospital Authority (HA) environment, this may be a logical starting point for piloting the public-private initiative in chronic disease management that Dr. Allen Cheung elaborated on in his theme speech.

For the first time in the history of the Pharmacy Conference, time was set aside for recent graduates in the two self-financed programs, pharmacy interns, and current postgraduate students to talk about their creative work. The two self-financed programs were Master of Clinical Pharmacy program and M.S. in Pharmaceutical Manufacturing and Quality program. This turned out to be a demanding assignment for the speakers given that they each had only 5 minutes to make their case and 2 minutes to field questions from two judges and attendees in the session. I was at the session on Pharmaceutical Manufacturing and Quality. All six speakers delivered flawless presentations and demonstrated superb command of the subject matter of the topic of their respective graduation project. Lorita P.S. Ho was judged to be the winner for her presentation on “Implementation of quality risk management in a Hong Kong pharmaceutical manufacturer for PIC/s GMP compliance.”

There were two winners in each of the other two parallel sessions. In the Practice session, the winners were Andy Chang for his presentation entitled, “Clinical implications of pharmacist interventions on drug administration for geriatric patients with dysphagia” and Sam Fong for his presentation entitled, “A study on the impact of a pharmacist-led neurology refill clinic: experience of a local hospital in Hong Kong”. In the Free Paper session, the two winners were Yung-ta Lin for his presentation entitled, “The impact of antibiotic stewardship program in Center-Taiwan hospital: A segmented time series analysis” and Chung-yuet Yu for her presentation entitled, “Implementation of pharmacist-managed medication review and reconciliation service in the orthopaedic ward at Queen Elizabeth Hospital.

The final hour-long plenary session was an update by representatives of the Task Force on Developing a Proposal in Establishing a Pharmacy Council in Hong Kong. Since the adjournment of the 2015 Pharmacy Conference on March 29, 2015, the Task Force refined the preliminary framework in preparation for the consultation phase. Details of such activities are reported elsewhere in this issue of the Journal. Professor the Honorable Joseph Lee, Chairman of the Health Panel at the Legislative Council, was invited to offer his legislative perspective. He cautioned the profession of the speed bumps ahead, such as the prevailing political climate in Hong Kong, the fact that the Pharmacy and Poisons Ordinance was amended not too long ago, and the appearance of a divided profession.

In accepting Professor Joan Zuo’s nomination to chair the 2016 Hong Kong Pharmacy Conference with a mandate to increase the visibility of science in the program, I was apprehensive of the possibility that science would not be highly valued, as would be reflected in a low number of paid registrations and/or sparse attendance at the “scientific” sessions. I was ecstatic to witness the excellent, evenly distributed turnout in every session throughout the day and a half conference, including the plenary session on Pharmacy Council at the very end. This was testament to the leadership of Dr. C.P. Lee and Ms. S.C. Chiang, Co-chairs of the Programming Sub-committee, in developing a roster of timely topics, pairing the topics with engaging speakers, and staging the topics seamlessly. It was an exhausting conference that had pushed our intellectual stamina to learn to the limit.

I would also like to acknowledge Mr. William Chui and Professor Vivian Lee, co-chairs of the Sponsorship Sub-

committee, for their superb effort in stimulating the interest of our partners in the private sector to support the 2016 Conference. Their enviable success was indicative of their credibility, celebrity status, and professional standing in the pharmacy circle in Hong Kong. To the 26 sponsors, I was touched by your generous support, which enabled us to invite 8 overseas speakers from Australia, Mainland China, the United Kingdom, and the United States of America, produce a conference mobile apps available to the delegates, and keep the conference registration fee low. The educational grant from Pfizer enabled the conference to waive the registration fee of the entire graduating pharmacy class in the two universities, 75 in all. The enthusiastic response from these future pharmacists to the announcement of complimentary registration is reassuring. The annual pharmacy conference needs their continuing support, and they in turn need forums like the pharmacy conference to stay intellectually sharp and professionally innovative. Looking into the future, an effective pharmacist of the 21st century is not only up-to-date on drug

product knowledge, but also skilled at coaching colleagues on the healthcare team in applying unique aspects of that knowledge space in caring for the patient. Only then will the right medicine is prescribed, dispensed, administered, consumed and monitored. This is the definitive outcome of practicing **“The Art and Science of Integrated Pharmacy Practice.”**

I look forward to meeting you again at the 2017 Conference on February 17-18, 2017.

Yours sincerely,



Vincent H.L. Lee
Chairman, Organizing Committee
Hong Kong Pharmacy Conference 2016

The Society of Hospital Pharmacists of Hong Kong (SHPHK) Office Bearers 2016/17

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The Scientific Meetings :

1. “Recent Advancement in Cancer Immunotherapy”
Speakers: Dr Joanne Chiu Clinical Assistant Professor, Department of Medicine, The University of Hong Kong, Queen Mary Hospital Miss Ritchie KWOK Chief Pharmacist, Hong Kong Integrated Oncology Centre
Date: 20th May 2016 (Friday)
Time: 6:30-6:55pm (Reception) 6:55-8:15pm (Lecture) 8:15-9:30pm(Dinner)
Venue: Shanghai Room 1, Level 8, Cordis, Hong Kong

2. “Gene Testing for Diseases and Drug Therapy Management”
Speaker: Dr Wing Chan
Date: 15th July 2016 (Friday)
Time: 6:30-7:15pm (Reception & Light Refreshment) 7:15-8:30pm (Lecture)
Venue: Ruttonjee Hospital Lecture Theatre

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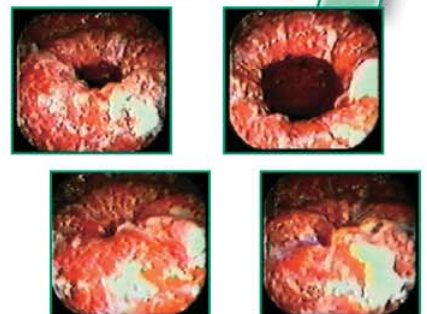
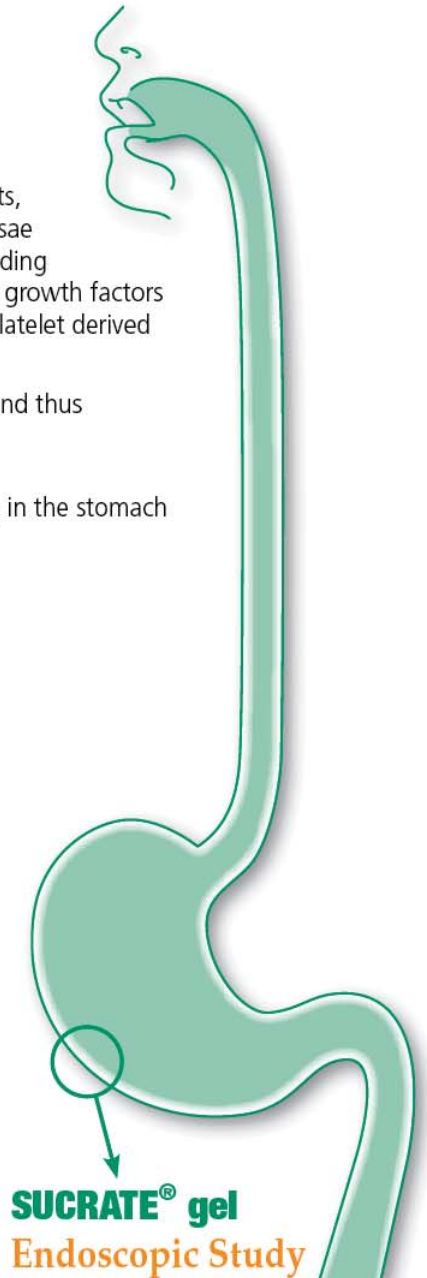
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Prepared and edited by Ivy Chan

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The medicinal product is intended for inhalation use only. The cartridge can only be inserted and used in the RESPIMAT® inhaler

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P1S1S3



MSc in Clinical Pharmacy* Application Code: 1450-HS073A

This is a 2-year part-time programme in HK delivered through face-to-face and distance learning. Tutorials / workshops are run by visiting academics from the University of Sunderland, U.K. The degree is awarded by the University of Sunderland.

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- Training in research skills
- High and timely completion rate

Teaching and Assessment:

Teaching is conducted through lectures, tutorials, seminars, group work and structured practical experience. Project work is required on a topic relevant to patients' needs from the students' area of study.

* This course is an exempted course under the Non-Local Higher and Professional Education (Regulation) Ordinance. It is a matter of discretion for individual employers to recognize any qualification to which this course may lead.

BSc (Hons) Pharmaceutical Science* Application Code: 1450-HS072A

This programme is a 2-year top-up degree offered in part-time mode of study in Hong Kong. The BSc (Hons) Pharmaceutical Science is to be awarded by the University of Wolverhampton, UK. The programme aims to produce high quality pharmaceutical science graduates with the generic, subject-specific and transferable knowledge and skills suited to a career in the pharmaceutical industry or other related laboratory based scientific discipline.

Programme Features:

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Abbreviations

About, approximately: ca.
Anhydrous: dry (not anhyd.)
Aqueous: aq.
Circular dichroism: CD
Concentrated (or mineral acids): conc.
Concentrations: ppm (or ppb), μM , mM, M, %, mol
Dry weight: dry wt; fresh weight: fr. wt
Electricity: V, mA, eV
Force due to gravity (centrifugation): g; rpm (revolutions min^{-1})
Gas chromatography: GC
Gas chromatography-mass spectrometry: GC-MS Trimethylsilyl derivative: TMSi (TMS cannot be used as this refers to the internal standard tetramethylsilane used in ^1H NMR)
High performance liquid chromatography: HPLC
Infrared spectrophotometry: IR
Length: nm, μm , mm, cm, m
Literature: lit.
Mass spectrometry: m/z [M]⁺ (molecular ion, parent ion)
Melting points: uncorr. (uncorrected)
Molecular mass: Da (daltons), kDa
Molecular weight: M_r
Nuclear magnetic resonance: ^1H NMR, ^{13}C NMR, Hz, δ
Numbers: e.g. 1, 10, 100, 1000, 10000; per or $^{-1}$
Optical rotatory dispersion: ORD
Paper chromatography: PC
Precipitate: ppt.
Preparative thin-layer chromatography: prep. TLC
Radioactivity: dpm (disintegrations per min), Ci (Curie), sp. act (specific activity), Bq (1 becquerel = 1 nuclear transformation sec^{-1})

Repetitive manipulations: once, twice, x3, x4, etc.
RR_t (relative retention time), R_i (Kovats' retention index), ECL (equivalent chain length- term frequently used in fatty acid work)
Saturated: satd.
Solution: soln.
Solvent mixtures including chromatographic solvents: abbreviate as follows n-BuOH-HOAc-H₂O (4:1:5)
Statistics: LSD (least significant difference), s.d. (standard deviation), s.e. (standard error)
Temperature: (with centigrade), mp, mps, mmp, bp
Temperature: temp.
Thin-layer chromatography: TLC, R_f
Time: s, min, h, day, week, month, year
Ultraviolet spectrophotometry: UV, A (absorbance, not aD-optical density)
Volume: l, (litre), μl , ml
Weight: wt, pg, ng, μg , mg, g, kg

Inorganics, e.g. AlCl₃ (aluminum chloride), BF₃ (boron trifluoride), Cl₂, CO₃, H₂, HCl, HClO₄ (perchloric acid), HNO₃, H₂O, H₂O₂, H₂SO₄, H₃BO₃ (boric acid), He, KHCO₃ (potassium bicarbonate), KMnO₄ (potassium permanganate), KOH, K-Pi buffer (potassium phosphate buffer), LiAlH₄ (lithium aluminium hydride), Mg²⁺, MgCl₂, N₂, NH₃, (NH₄)₂SO₄, Na⁺, NaBH₄ (sodium borohydride), NaCl, NaIO₄ (sodium periodate), NaOH, Na₂SO₃ (sodium sulphite), Na₂SO₄ (sodium sulphate), Na₂S₂O₃ (sodium thiosulphate), O₃, PPI (inorganic phosphate), SO₄²⁻, Tris (buffer).

Organics, e.g. Ac₂O (acetic anhydride), n-BuOH (butanol), C₆H₆ (benzene), CCl₄ (carbon tetrachloride), CH₂Cl₂ (methylene chloride), CHCl₃ (chloroform), CH₂N₂ (diazomethane), CM (carboxymethyl), DEAE (diethylaminoethyl), DMF (dimethylformamide), DMSO (dimethyl sulphoxide), EDTA (ethylene-diaminetetra-acetic acid), Et₂O (diethyl ether), EtOAc (ethyl acetate), EtOH (ethanol), HCO₂H (formic acid), HOAc (acetic acid), iso-PrOH (iso-propanol), Me₂CO (acetone), MeCOEt (methyl ethyl ketone), MeOH (methanol), NaOAc (sodium acetate), NaOMe (sodium methoxide), petrol (not light-petroleum or petroleum ether), PhOH (phenol), PrOH (propanol), PVP (polyvinylpyrrolidone), TCA (trichloroacetic acid), TFA (trifluoroacetic acid), THF (tetrahydrofuran).
 ^1H NMR solvents and standards: CDCl₃ (deutero-chloroform), D₂O, DMSO-d₆ [deuterodimethylsulphoxide not (CD₃)₂S], pyridine-d₅ (deuteropyridine), TMS (tetramethylsilane).

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FINDING A NEW EQUILIBRIUM

IN MAJOR DEPRESSIVE DISORDER



- Recommended 1st-line treatment for MDD¹
- Low potential for CYP2D6-mediated drug interactions²⁻⁴
- Discontinuations due to adverse events similar to placebo⁵
- Safety profile comparable to placebo⁵⁻⁷
- Long-term use significantly lowers rate of relapse compared to placebo⁶
- Improves well-being and functioning⁸⁻⁹



References 1. Law R, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy. *J Affect Disord* 2009;117(Suppl 1):526-43. 2. Preskorn S, et al. Comparison of the pharmacokinetics of venlafaxine extended release and desvenlafaxine in extensive and poor cytochrome P450 2D6 metabolizers. *J Clin Psychopharmacol* 2009;29:39-43. 3. Nichols AJ, et al. Pharmacokinetics of venlafaxine extended release 75 mg and desvenlafaxine 50 mg in healthy CYP2D6 extensive and poor metabolizers: a randomized, open-label, two-period, parallel-group, crossover study. *Clin Drug Investig* 2011;31:155-167. 4. Preskorn SH, et al. Effect of desvenlafaxine on the cytochrome P450 2D6 enzyme system. *J Psychiatr Pract* 2008;14:368-378. 5. Pristiq® (desvenlafaxine) Prescribing Information. Pfizer Corporation Hong Kong Limited: version January 2011. 6. Rosenthal J, et al. Efficacy and safety of desvenlafaxine 50 mg/day for prevention of relapse in adult outpatients treated for major depressive disorder. Presented at: The 165th Annual Meeting of the American Psychiatric Association (APA), 5-9 May 2012, Philadelphia, USA. 7. Clayton A, et al. An evaluation of sexual function in employed outpatients with major depressive disorder treated with desvenlafaxine 50 mg or placebo. *J Sex Med* 2013;10:768-776. 8. Boyer P, et al. Efficacy, safety, and tolerability of fixed-dose venlafaxine 50 and 100 mg/day for major depressive disorder in a placebo-controlled trial. *Int Clin Psychopharmacol* 2008;23:243-253. 9. Soares CN, et al. Assessing the efficacy of desvenlafaxine for improving functioning and well-being outcome measures in patients with major depressive disorder: a pooled analysis of 9 double-blind, placebo-controlled, 8-week clinical trials. *J Clin Psychiatry* 2009;70:1365-1371

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TRADE NAME: PRISTIQ® **PRESENTATION:** 50 mg, light pink, square (pyramid-one sided) tablet debossed with "W" "50" on the flat side. **INDICATIONS:** Treatment of major depressive disorder (MDD). **DOSE & ADMINISTRATION:** 50 mg once daily at approximately the same time, with or without food. The recommended dose in patients with severe renal impairment or end-stage renal disease (ESRD) is 50 mg every other day. Supplemental doses should not be given to patients after dialysis. **CONTRAINDICATIONS:** Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Pristiq formulation. Must not be used concomitantly in patients taking monoamine oxidase inhibitor (MAOI) or in patients who have taken MAOIs within the preceding 14 days. **WARNINGS & PRECAUTIONS:** All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behaviour, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Not approved for use in treating bipolar depression; Serotonin syndrome or Neuroleptic Malignant Syndrome-like reactions; Activation of mania/hypomania; Elevated blood pressure & abnormal bleeding; Serum cholesterol & triglyceride elevation; Narrow-angle glaucoma; Renal impairment; Seizure; Hyponatremia; Interstitial lung disease & Eosinophilic pneumonia; New symptoms and serious discontinuation symptoms were reported in discontinuation of treatment; Caution is advised to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders; Co-administration of drugs containing desvenlafaxine & venlafaxine is not recommended. **INTERACTIONS:** Risk in combination with other CNS-active drugs; MAOI; Serotonergic drugs; Drugs that interfere with hemostasis; Alcohol; Concomitant use with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq; Minimal inhibitory effect of desvenlafaxine on CYP2D6. **PREGNANCY AND LACTATION:** Pregnancy Category C. Carefully consider the potential risks and benefits of treatment when treating a pregnant woman during pregnancy especially in the third trimester, labor and delivery. Only breastfeed if the expected benefits outweigh any possible risk as desvenlafaxine is excreted in human milk. **SIDE EFFECTS:** Most commonly observed adverse reactions in short-term fixed-dose studies were: nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders. Hypersensitivity, effects on blood pressure, abnormal bleeding, mydriasis, hypomania & mania, serum cholesterol & triglyceride elevation, and seizure were also reported. **DRUG ABUSE AND DEPENDENCE:** Not systematically studied in preclinical/clinical studies for its potential for abuse. Physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Pristiq. Limited clinical experience with desvenlafaxine succinate overdose in humans. Reference: HK PI (Version Date JAN2011) Date of preparation: JUL2012 Identifier number: PRI50712

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