Clinical Pharmacology
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The Cover Shot

The cover shows a two-year-old American shorthair. In American homes, there are more cats than children! Cats have long been domesticated and were mummified in Ancient Egypt. Cats have superhuman abilities, such as seeing in the dark, hearing ultrasound and leaping roof-to-roof. They are quiet; they move around in silence and do not bark. The lifespan of cats has increased like humans. Thus, cats increasingly die of diseases of ageing such as cancer and kidney failure. Moreover, inbreeding has led to genetic disorders such as polycystic kidney disease and hypertrophic cardiomyopathy. Therefore, study of cats benefits both cats and humans.

Prof Bernard MY CHEUNG
First Vice-President
The Federation of Medical Societies of Hong Kong
This issue of the Medical Diary is devoted to clinical pharmacology. It may seem like a specialist topic, but in fact, it is very wide and covers a large chunk of medicine, as the diverse articles in this issue illustrate. In the era of the COVID-19 pandemic, the importance of clinical pharmacology, and the discipline it represents, has never been so prominent. What is the treatment for COVID-19? How are new drugs found and how can they be evaluated for their efficacy and safety? How do you evaluate the efficacy and safety of vaccines? How do you judge whether an adverse event is related or unrelated to a drug or vaccine? These are the kind of questions to which clinical pharmacology provides the framework for addressing. On the part of the general public, never has the public discussed and debated so avidly efficacy and safety, adverse effects, the need for phase 3 clinical trials and so on. What seems dry and academic has become controversies on television, radio, internet and newspapers, and the stuff of everyday conversation.

In this issue, there is a discussion of what is or is not drug allergy by Dr Philip Li. Dr Patrick Leung writes on the latest recommendations on how to sedate the agitated patient. Prof Cyrus Kumana and Dr Harry Gill recall how the locally-discovered award-winning arsenic-based treatment for cancer was developed. Dr Joanne Chiu takes us through the complexities of new therapies for breast cancer, while Dr Elaine Chow takes us through the range of exciting new therapies for type 2 diabetes mellitus. Dr CL Cheung, a pharmacologist, reviews for us osteoporosis, a condition with increasing prevalence due to an ageing society lacking physical activity.

This issue of the Medical Diary is refreshingly different, because instead of focusing on an organ or disease, the spotlight is turned on drugs. Most of the undergraduate and postgraduate training in Medicine is about diagnosis, investigation and management. Even in postgraduate training, there is not much emphasis on the choice of drugs, and understanding their properties, including the harms as well as the benefits. As the Editor of this issue, I hope to kindle interest in this pervasive but inconspicuous speciality. I sincerely thank all the authors, who toiled tirelessly for this special issue, and the industrial partners for their unflinching support.
THIS IS AIMOVIG. THIS IS HEAD-TO-HEAD DATA. THIS IS PREVENTION

MORE DAYS WITHOUT MIGRAINE FOR MORE PATIENTS

- Significantly reduces migraine frequency and severity\(^1\)
- Results may even improve over time among responders\(^2,4\)

MORE YEARS OF EVIDENCE THAN EVER BEFORE

- Evaluated to 5 years in the longest-running study of an anti-CGRP\(^4\)
- Most experience in the real world\(^5,7\) and results in this setting may exceed those seen in trials\(^6,9\)

MORE CONFIDENCE FOR SIMPLE MANAGEMENT

- Proven superiority over topiramate for patient adherence, efficacy and quality of life\(^1\)

\(^1\) Among responders continuing on Aimovig, the percentage who cut their MMDs in half increased from 46% at 3 months, to 65% at 1 year and 69% at 5 years.\(^3\)

\(^4\) CGRP, Calcitonin Gene-Related Peptide, MMDs, Monthly Migraine Days

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Oral Arsenic Trioxide Treatment for Acute Promyelocytic Leukaemia: A Novel Treatment Strategy Facilitated by Clinical Pharmacology

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Conflict of interest declarations

The University of Hong Kong holds the following patents on oral arsenic trioxide:

1. Oral arsenic trioxide for treatment of leukaemia (US patent 7,521,071 B2)
2. Oral arsenic trioxide for treatment of leukaemia (Japan patent 4786341)
4. Formulation of oral compositions comprising arsenic trioxide (EP 1562616 B1)
5. Oral arsenic trioxide for treatment of rheumatoid arthritis (Japan patent P6049455)
6. Oral arsenic trioxide for treating inflammatory arthritis (US patent 10,092,595 B2)

CR Kumana, YL Kwong and H Gill are employees or associated with the University of Hong Kong. They have no other relevant conflicts of interest to declare. R Mak has no relevant conflicts of interest to declare.

The tentacles of Clinical Pharmacology (the scientific study of drugs and their impact in clinical situations) spread far and wide. In that context, they impinge on issues that include: therapeutic efficacy and safety, pharmacology, toxicology, pharmacokinetics, pharmacodynamics, clinical trial methodology, drug treatment guidelines and appropriately targeted education, the manufacture of pharmaceuticals, cost-effectiveness considerations, and public health. Beyond these, they also involve government drug-regulatory authorities and hospital drug advisory committees, medication error surveillance and medicolegal disputes, the study of medication utilisation and prescribing (including drug treatment records), as well as a multitude of ethical conundrums. Notably, the Clinical Pharmacology story described in this article has ramifications in virtually all the aforementioned aspects of drug usage.

ARSENIC TRIOXIDE AS A THERAPEUTIC AGENT

Despite arsenicals having been around for several millennia, their role as genuinely effective haematological medicines has only been recognised during the last hundred and fifty years, and unsurprisingly the fascinating and checkered history of such developments has been the focus of several reviews.13 Thus, whilst arsenic and its compounds are well documented as a means of poisoning, they were also purported to have numerous therapeutic properties. Arsenicals were probably introduced into Western Medicine around the eighteenth century. One such ‘medicine’ was Fowler’s solution (also called Liquor Arsenicalis), which was a relatively crude, orally imbibed liquid formulation containing arsenic trioxide. In the late nineteenth century, reports from Germany and the US indicated that this orally taken medication was useful in the treatment of certain chronic leukaemias. Thereafter, it became a primary anti-leukaemic therapy used widely for this purpose for many decades, but its utility was always limited by its toxicities. Moreover, due to the advent of chemotherapy and radiotherapy after the Second World War, resorting to oral arsenic to treat leukaemias was gradually phased out. In the mid twentieth century though, new reports from Harbin in Mainland China described consistently promising haematologic responses in patients with acute promyelocytic leukaemia (APL) treated with intravenous arsenic trioxide (IV ATO). Reports from other nations soon followed and confirmed these observations. Such findings also appeared to be consistent with in-vitro studies describing ATO-induced apoptosis and differentiation of APL cells. Furthermore, around that time, molecular genetic advances showed that APL was almost always associated with a specific chromosomal translocation, leading to the formation of an oncogenic fusion protein PML-RARA.4 Notably, this molecular aberration identified patients responding more favourably to all-trans retinoic acid (ATRA) and ATO than to conventional regimens combining ATRA and chemotherapy. Later studies showed that arsenic is bound directly to the PML-RARA oncoprotein to enhance its degradation. Based on these discoveries

1 Study of how the body handles/disposes of a given drug, over periods of time.
2 Study of a given drug impacts/influences the body (or tissues), over periods of time.
3 t(15;17)(q24;q21)
as well as on clinical trial findings, IV ATO treatment gained US Food and Drug Administration (FDA) therapeutic approval and became recognised as an important therapeutic tool for the management of patients with APL.

Nevertheless, recourse to repeated 4 to 8 week courses of daily IV ATO infusions posed many challenges that seriously impeded patient quality of life. These challenges included: inconvenience (inevitably entailing hospitalisation and its attendant costs), cumbersome paraphernalia for intravenous infusion and maintaining vascular access, and prohibitive drug costs; currently, one month’s typical treatment can retail at in excess of US$ 11,000.

REJUVENATION OF ORAL ARSENIC TRIOXIDE

Based on what was known about the Hong Kong experience, local haematologists trolled through the meticulously written hospital case notes of local patients treated with Fowler’s solution in the 1950s. The latter records consistently yielded objective clinical benefits as well as improved blood counts. These observations prompted a re-evaluation of a possible role for oral ATO to treat APL patients with a formulation prepared in accordance with Good Manufacturing Practice (GMP). Compared to IV dosing, oral treatment had the potential of conferring important quality of life benefits for patients, namely: greater convenience (enabling home treatment), avoidance of intravenous interventions, and huge savings in drug and other ancillary costs. Conceivably, therefore, such benefits might all be achieved with a degree of confidence and safety that was never attained with Fowler’s solution.

These considerations prompted the development of a pure ATO solution for oral use, coupled with determination of its systemic bioavailability. The problems posed by this undertaking and how they were addressed/overcome (with the collaboration of hospital pharmacists) are outlined in Table 1. A comparison of arsenic bioavailability following IV and oral treatment is illustrated in Fig. 1 and its legend, and a summary of the main findings and their derivation is shown in Table 2 and its legend. A detailed account of this study and its findings was published in 2002, and showed that the systemic bioavailability estimates of arsenic attributable to each route of administration were essentially the same.

SUBSEQUENT DEVELOPMENTS

Having demonstrated that the oral ATO solution produced in Hong Kong (registered commercially as Arsenol™) and the commercially used IV formulation had comparable bioavailability, local haematologists began prescribing the newly produced oral formulation to APL patients. Furthermore, they used the same conventional daily dosages (typically 10 mg/day or 0.15mg/kg/day) as had been used parenterally. Compared with IV dosing, the new oral preparation was found to be at least as effective, safe, and well tolerated, and yet much more convenient and easier for patients to take; at the same time it was undoubtedly much more

### Table 1. Production & Bioavailability Determination of an Oral As2O3 Formulation

<table>
<thead>
<tr>
<th>Problem</th>
<th>How Addressed/Overcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Securing Institutional Ethics Committee approval for the study protocol</td>
<td>The proposed unconventional bioavailability study protocol was approved based on the following compelling arguments: 1) All recruited patients would have a disease for which treatment with As2O3 would be indicated. 2) Each patient would need to give written informed consent. 3) Recruiting healthy volunteers to take arsenic would prove daunting and notable to reveal how the oral formulation was tolerated by sick diseased patients. Obtained from Sigma (USA).</td>
</tr>
<tr>
<td>Sourcing pharmaceutical grade As2O3 (ATO) powder</td>
<td>The suspension’s pH was manipulated to 7.2 to yield a clear colourless solution containing 1 mg/ml of As2O3. Contrary to some recommendations, no fungicide was added as the entire preparation was conducted in a pharmaceutical isolator. Subsequent microbiology and chemical testing of samples yielded no fungi and an unchanged solute concentration exceeding one year (indicative of its minimum shelf-life).</td>
</tr>
<tr>
<td>Bioavailability testing in sick hospitalised patients precluded a conventional crossover design, blinding, or tolerability assessment.</td>
<td>In all, 9 patients were recruited using predefined inclusion/exclusion criteria and asked to refrain from seafood (an arsenic source) in the preceding week. Each patient received a 10mg IV infusion of As2O3 over 1 hour on day 1, followed by a 10mg oral dose 24 hours later. Just before initiating IV dosing and at predefined times over the next 48 hours, venous blood samples were drawn for determination of plasma and whole blood arsenic concentrations.</td>
</tr>
</tbody>
</table>

### Table 2. Area Under the Curve (AUC) of Plasma Arsenic Concentrations/Time Plots (Nanomolar-hours) (Adapted from Table 2 in Kumana et al.

<table>
<thead>
<tr>
<th>Mean ± SEM</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 (0-24 h) AUC attributed to IV Dose</td>
<td>2673 ± 262</td>
</tr>
<tr>
<td>Day 2 (24-48 h) AUC attributed to Oral Dose</td>
<td>2640 ± 343</td>
</tr>
</tbody>
</table>

For each of the 9 study patients, plasma arsenic concentration versus time plots from 0 to 48 hours (see fig. 1) were inscribed, and corresponding AUCs were derived using standard computer software (GraphPad Prism Version 3) incorporating the trapezoidal rule. The 0 to 24 h AUCs were regarded as attributable to IV dosing on day 1. The difference between the gross 24 to 48 h AUC and that extrapolated for the day 2 decay in levels ensuing after IV dosing on day 1, was regarded as the AUC attributable to oral dosing between 24 and 48 hours. Respective AUCs for each patient (post IV dosing on day 1 and attributable to oral dosing on day 2) were taken to be measures of immediate arsenic bioavailability attributable to each formulation.

**Fig. 1. Area Under the Curve (AUC) of arsenic levels attributed to intravenous and oral dosing of arsenic trioxide in a single patient (nanomolar-hours). [Adapted from Kumana et al with permission]**
cost and time effective to deliver. Others also reported similar findings with subsequently developed (though differently prepared) oral formulations. Interestingly, ATO given IV has been repeatedly linked to the occurrence of dangerous cardiac arrhythmias (Torsades de Pointes) and sudden death, and it seems that this risk is largely mitigated when using the oral route. This added advantage of oral dosing, formed the basis for securing a US patent for the treatment of APL patients with the Hong Kong produced oral As$_2$O$_3$ formulation, and soon after, similar patents were also granted from other parts of the world.

In the ensuing years, numerous phase II trials have been conducted using oral ATO treatment with and without other active agents (including ATRA, ascorbic acid, and a plethora of various chemotherapeutic agents), some of which may act synergistically with arsenic. The latter investigations confirmed the long-term efficacy and safety of oral ATO used instead of IV dosing to be a suitable treatment strategy for maintaining patients in remission and improving disease free survival as well as overall survival. Compared with IV dosing moreover, these benefits were achieved with much less quality of life disruption and at a much lower cost. More recent studies in newly diagnosed or relapsed APL patients have shown that when oral ATO is incorporated into induction and re-induction regimens, excellent long-term outcomes and cure can be achieved.

In Hong Kong, Arsenol® packaged as shown in Fig. 2, together with an updated package insert in English and Chinese - is being produced by a local manufacturer (Jacobson Pharma Corporation Ltd). Moreover, the Hong Kong Department of Health and the Hong Kong Hospital Authority have approved Arsenol®’s registration, with a caveat that its use was to be part of an agreed territory-wide service, coordinated by a single tertiary hospital haematology centre. Furthermore, there could also be a role for ATO treatment for patients with other haematological and non-haematological disorders, including: nucleophosmin 1 (NPM1)-mutated acute myeloid leukaemia (AML), lymphoma, and lung cancer, as well as certain autoimmune disorders. If these possibilities are borne out, the same advantages are likely to ensue for oral as opposed to IV dosing as apply to APL.

CONCLUSION

This article describes the production of a high quality oral ATO formulation (Arsenol®) facilitated by Clinical Pharmacology input, which has been approved to treat patients by the Hong Kong Department of Health and the Hong Kong Hospital Authority. Consequently, local APL patients treated with this oral preparation can enjoy the same therapeutic efficacy as those receiving IV doses, but with the added benefits of far more convenience (enabling home treatment), greater affordability, and lower risks of cardiotoxicity. For individual patients and societies at large, the latter advantages can be regarded as important and genuinely life-changing and cost-saving. Moreover, it is anticipated that in the not-too-distant future - this highly effective, inexpensive, and convenient form of treatment will become more widely available commercially around the world. Ironically, stemming from the therapeutic developments described here, APL that was once regarded as among the most malignant and costly to treat leukaemias - has now become among the most curable and affordable to confront conveniently with oral therapy.

References

Arsenol Oral Solution* is indicated for the treatment of Acute Promyelocytic Leukaemia (APL) with the bioequivalence to its injectable counterparts offering:

- Superior safety profile
- Reduced hospitalization
- Considerable reduction of overall treatment cost
- Superior quality-of-life for patients
- First-line treatment for APL patients in Hong Kong

*First-Ever Patented Prescription Drug Developed in HKSAR

Oral arsenic trioxide is the world's first oral formulation of Arsenic Trioxide and also the first prescription drug ever developed in Hong Kong securing US and EU patents.

Research pioneered by Prof Yik-Lam Kwong and Dr Harry Gill of the Department of Medicine, the University of Hong Kong, has shown oral arsenic trioxide to be highly efficacious in acute promyelocytic leukaemia (APL). In Hong Kong, oral arsenic trioxide has become the standard for frontline induction for newly diagnosed APL, for maintenance of remission and for patients in relapse.

More than 300 patients with APL have since been treated, with excellent results. The use of oral arsenic trioxide has replaced bone marrow transplantation in relapsed APL. Oral arsenic trioxide has also been used in the treatment of other blood cancers, including lymphomas and myeloma.
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*NMPA: National Medical Products Administration
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Current Treatment for Metastatic Breast Cancer

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University of Hong Kong
Queen Mary Hospital,
& Gleneagles Hospital Hong Kong

INTRODUCTION

Breast cancer is the most common female cancer in Hong Kong, affecting 1 in 14 women in their lifetime1. Although the majority of breast cancer is diagnosed at an early stage when curative resection is feasible, the cancer recurs in many patients and causes death. The prognosis and outcome of patients with metastatic breast cancer rely on effective drug therapy that can both prolong survival and improve the quality of life.

Drug treatment for metastatic cancer is determined by the phenotypes. Based on the overexpression of hormone-receptors and epidermal growth factor receptor type 2 (HER2), breast cancer can be divided into HER2-positive, hormone receptor (HR)-positive, or triple negative breast cancer (Fig. 1).

HER2-POSITIVE BREAST CANCER

HER2-positive breast cancer is an aggressive subtype, constituting about 1/3 of all breast cancer. Since the development of the first anti-HER2 targeted therapy two decades ago, there has been tremendous progress in drug development for this disease. Fig. 2 summarises the development of anti-HER2 treatment by their year of approval by the U.S. Food and Drug Administration (FDA). The first anti-HER2 therapy is trastuzumab, a large-molecule antibody, which works by binding to the HER2 receptor on the surface of breast cancer cells and blocking the downstream growth signalling. Trastuzumab can also activate antibody-dependent cellular cytotoxicity (ADCC); thus it interplays with the immune system in fighting cancer. Many subsequent anti-HER2 treatments are built on trastuzumab. For instance, pertuzumab blocks hetero-dimerisation of HER2 and HER3 surface receptors and facilitates the efficacy of trastuzumab. Addition of pertuzumab to trastuzumab-based treatment prolonged the progression-free survival by 6 months, and reduced death by 34%2. Trastuzumab emtasine (T-DM1), the first antibody-drug conjugate (ADC) that links trastuzumab to chemotherapy, works like targeted chemotherapy and offers the advantage of both drugs without the typical toxicities of chemotherapy. It also significantly reduced progression and death, as compared with the standard of care3. The second ADC, trastuzumab deruxtecan (TDxD) is now available. It has a stronger chemotherapy partner and could shrink HER2-positive breast cancer in half of the patients who have progressed on existing standard-of-care anti-HER2 therapy4. The effect on overall survival is not known yet. Anti-HER2 therapy also comes in oral form. These are small-molecule tyrosine kinase inhibitors that can bind to an intracellular area of tumour cells. Due to their small size, they have appreciable activity for patients with brain metastasis5-6. As the patent for...
the branded trastuzumab has expired, we have seen a number of generic formulations of this drug in the market recently. The treatment of HER2-positive breast cancer is becoming more affordable.

HORMONE RECEPTOR-POSITIVE BREAST CANCER

Around 60-70% of breast cancer belongs to hormone receptor (HR)-positive subtype. This subtype tends to be more slowly growing and many patients can survive for many years. In the absence of excessive tumour burden threatening organ function, hormonal therapy would be the standard of care until the disease becomes resistant to available hormonal therapy. Most patients would receive hormonal therapy, be it selective estrogen-receptor response modulators (e.g. tamoxifen), aromatase inhibitor (AI), or estrogen receptor degrader, as a single agent or in the combination with cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors. There are now 3 CDK4/6 inhibitors on the market — palbociclib, ribociclib, and abemaciclib. CDK4/6 inhibitors have revolutionised the treatment of HR-positive breast cancer. Not only can they prolong the use of hormonal therapy and decrease the chance of progression by close to 50%, but some of them have also already been proven to prolong the overall survival in these patients7,8. Upon disease progression while on these agents, clinicians will resort to molecular testing of the tumour, and to explore if the patients would be candidates for targeted agents such as phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3CA) antagonist (e.g. alpelisib)9, or Poly(ADP-ribose) polymerase-1 (PARP) inhibitor (e.g. olaparib, talazoparib)10,11. For patients who have exhausted all treatment using hormonal therapy or targeted agents, or for those patient who have heavy tumour burden with visceral crisis, chemotherapy would be used to stabilise the disease. Fig. 3 summarises the algorithm for the treatment of metastatic HR-positive breast cancer.

TRIPLE NEGATIVE BREAST CANCER

Triple negative breast cancer (TNBC) is an aggressive breast cancer. It carries a poorer prognosis than the other two forms of breast cancer. The average overall survival is 12 to 18 months only. Molecularly it is heterogeneous yet most are ‘basal-like’ and of higher grade. Chemotherapy is the mainstay treatment traditionally. Patients rotate from one chemotherapy regimen to another one until complete resistance. The advance of immunotherapy with checkpoint inhibitor, such as atezolizumab or pembrolizumab, showed preliminary effect in the treatment of TNBC before12,13. However, due to inconsistency in longer-term outcome results, the indication of atezolizumab in TNBC was withdrawn by the company recently. Pembrolizumab remained an approved option for locally advanced TNBC at the moment with significant improvement in the pathological complete response14. When patients present with TNBC at young age, with the bilateral or contralateral disease, or known family history of breast cancer, the presence of germline mutation in breast cancer gene 1 (BRCA 1) or BRCA 2 mutation must be considered. Patients who carry this mutation can receive poly adenosine diphosphate-ribose polymerase (PARP) inhibitor as part of their treatment10,11 and currently it is the only oral targeted therapy available for TNBC. Most recently, antibody-drug conjugate (ADC) also plays a role in the treatment of TNBC. Sacituzumab govitecan is a monoclonal antibody against trophoblast cell-surface antigen (TROP)-2 coupled with a chemotherapeutic agent. It has been granted accelerated approval by the U.S. FDA for patients with metastatic TNBC who have received at least 2 prior therapies. Patient on this drug achieved median overall survival of 12.1 months compared with 6.7 months of the control arm15.

SUMMARY

Treatment of metastatic breast cancer depends on the phenotype. Although chemotherapy can be used in all subtypes, the use of targeted therapy is becoming increasingly important, and genetic testing should be considered when appropriate. The use of antibody-drug conjugate in both HER2-positive and TNBC is anticipated in the near future.

References

**Radiology Quiz**

**Dr Carol PY CHIEN**
MBBS, FRCR

**Questions**
1. What is the diagnosis?
2. What is the next step of investigation?
3. What are the possible complications?
4. What are the CT radiological signs of MCA cerebral infarct?

(See P.36 for answers)
ATTR-CM, a life-threatening and progressive disease that is widely and frequently underdiagnosed\textsuperscript{1,2}

25% of adults aged 80 years or older were found to have significant myocardial TTR amyloid deposition at autopsy\textsuperscript{2}

What is ATTR-CM?\textsuperscript{2}

- A type of cardiac amyloidosis
- Can occur as either wild type or hereditary type
- Progressive and life-threatening
- When the protein transthyretin misfolds, fibril deposits build up in the heart causing ATTR-CM

Please click the link below or scan the QR code to learn more about ATTR-CM and how you can save the lives of potential ATTR-CM patients
www.vyndamax.com.hk

The following Red Flags warrant your immediate attention\textsuperscript{2-4}:

**Cardiac:**

- HFpEF\textsuperscript{2}
- LFH on Echo\textsuperscript{2}
- Imaging and ECG discrepancy\textsuperscript{2} "Imaging finding of LVH and normal/low QRS voltage on ECG"

**Non-cardiac:**

- Orthopaedic syndromes (e.g. carpal tunnel syndrome, lumbar spinal stenosis and bicep tendon rupture)\textsuperscript{2}
- Polyneuropathy\textsuperscript{2}
- Family history of TTR amyloidosis\textsuperscript{4}

Abbreviations: ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin-receptor blockers; ATTR-CM: Transthyretin amyloid cardiomyopathy; BB: Beta blockers; ECG: Electrocardiogram; Echo: Echocardiography; HF: Heart failure; HFpEF: Heart failure with preserved ejection fraction; LVH: Left ventricular hypertrophy; TTR: Transthyretin.


VYNDAMAX ABBREVIATED PRESCRIBING INFORMATION

1. TRADE NAME: Vyndamax™ capsules (Tafamidis 61 mg). 2. PRESENTATION: 61mg soft capsules. 3. INDICATIONS: Vyndamax is indicated for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) \textsuperscript{3}. 4. DOSAGE: The recommended dose is one capsule of Vyndamax 61 mg (Tafamidis) orally once daily. 5. CONTRAINDICATIONS: Hypersensitivity to the active substances or to any of the excipients of the drug. Please refer to the full prescribing information for details. 6. WARNINGS & PRECAUTIONS: Women of childbearing potential should use appropriate contraception when taking tafamidis and continue to use appropriate contraception for 1 month after stopping treatment with tafamidis. Tafamidis should be added to the standard of care for the treatment of patients with transthyretin amyloidosis. Physicians should monitor patients and continue to assess the need for other therapy, including the need for organ transplantation, as part of this standard of care. Tafamidis should be discontinued in patients who undergo organ transplantation. 7. INTERACTIONS: Substrates of efflux transporter BCRP (breast cancer resistant protein, e.g. methotrexate, rosuvastatin, imatinib); substrates of uptake transporters OAT1 and OAT3 (organic anion transporters); e.g., non-steroidal anti-inflammatory drugs, bumetanide, furosemide, levoxadine, mexitetrad, oseltamivir, tenoxicam, ganetetox, adenosine, dideoxy, zidovudine, zalcitabine). 8. PREGNANCY AND LACTATION: Tafamidis is not recommended during pregnancy and in women of childbearing potential not using contraception. Tafamidis should not be used during breast-feeding. 9. SIDE EFFECTS: Palpitations and liver function test increased.

A causal relationship has not been established. Reference: Prescribing Information HK P1 (Version: Jul 2020) Date of preparation: Nov 2020 Identifier number: VYNX120. FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.
Primary Prevention of Osteoporosis in Hong Kong: A Brief Update

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INTRODUCTION

Osteoporosis is a prevalent disease especially among the elderly. Compared to other chronic diseases of the aged, osteoporosis receives little attention not only among the general public, but also among healthcare professionals. Unlike many other diseases, osteoporosis could be totally asymptomatic, and is therefore commonly described as a silent disease. Patients may only realise the presence of osteoporosis when they sustain a fracture. Among all osteoporotic fractures, hip fracture is known to be associated with the highest risk of morbidity, immobility, and mortality. According to our recent projection in Asia, if the incidence of hip fracture remains unchanged, there will be more than 25,000 hip fractures happening every year in Hong Kong by 2050, which will lead to an annual direct medical cost of more than 1.8 billion Hong Kong dollars. Knowing that Hong Kong holds the highest life expectancy in the world, it is an urgency to prepare for the “fracture tsunami” in Hong Kong.

OSTEOPOROSIS SCREENING

To reduce fracture-associated burden, primary prevention is of public health importance. In 2019, several non-governmental organisations, including Osteoporosis Society Hong Kong (OSHK), Society of Hospital Pharmacists of Hong Kong, Health in Action, Osteoporosis Concern Group, Silveriders, and Department of Pharmacology and Pharmacy, the University of Hong Kong, formed “The Osteoporosis Primary Care Task Force”. The Task Force aims to promote universal Dual-energy X-ray absorptimetry (DXA) screening to reduce the burden of osteoporotic fracture. Since universal DXA screening may not be cost-effective, our research team recently developed a simple 3-question questionnaire called Chinese Osteoporosis Screening Algorithm (COSA) to predict risk of osteoporosis, incorporation of COSA in osteoporosis screening may improve cost-effectiveness. COSA was developed using the data from the Hong Kong Osteoporosis Study, the first ever osteoporosis cohort study of all ages in Asia, and the data should have a high generalisability to the Hong Kong population. Based on our on-going validation study, the positive predictive value was approximately 0.5, meaning that ~50% of the “high risk patients” suggested by the COSA questionnaire are osteoporotic. This simple screening tool is expected to largely reduce the number of people requiring DXA scans, and to facilitate the implementation of population-wide screening. The pilot testing of COSA and its related management protocol has been implemented in Kwai Tsing District Health Centre (DHC). The incorporation of this protocol in future DHCs may play an important role in primary prevention of osteoporosis. In Hong Kong, since the mean age of hip fracture is approximately 82.1 years, reaching out to the “oldest old” (defined as people aged 80 or above) is important. Recently, a risk score (Hong Kong Osteoporosis Study [HKOS] score) has also been developed to predict fracture risk in the oldest old. This risk score seemed to have out-performed other risk scores, like FRAX and QFracture. Given that the HKOS risk score targets the most vulnerable population with the highest risk of hip fracture, the application of this risk score in predicting hip fracture may be clinically relevant in reducing hip fracture in Hong Kong.

PHARMACOLOGICAL INTERVENTION

Management of osteoporosis can be broadly categorised into pharmacological (Table 1) and non-pharmacological interventions (Table 2). In terms of pharmacological intervention, alendronate is the first-line medication commonly used to treat osteoporosis in Hong Kong. Our recent studies showed that alendronate and other nitrogen-containing bisphosphonates could potentially reduce the risk of incident cardiovascular diseases and pneumonia. These observations are in line with a subsequent large-scale randomised controlled trial. Nevertheless, poor treatment adherence of alendronate reduces the significance of the drug in fracture prevention. Newer non-oral medications, e.g., zoledronate and denosumab that only require intravenous infusion once a year or subcutaneous injection twice a year, may enhance treatment adherence and lead to a better treatment outcome.

For those with severe osteoporosis, promotion of bone formation is required to build stronger bone effectively, instead of purely depending on inhibition of bone resorption. Thus, anabolic agents are recommended for patients with severe osteoporosis at high risk of fracture. Currently, there are two anabolic agents available in
Hong Kong. The first anabolic agent available in the market is teriparatide, which is a recombinant human parathyroid hormone (PTH) 1-34. Daily subcutaneous injection of teriparatide leads to the anabolic window of PTH-signaling, which allows the net gain of bone formation. However, while teriparatide has a significant effect in improving Bone Mineral Density (BMD) at the lumbar spine, its effect on hip BMD, and hence hip fracture prevention, is controversial. On the other hand, romosozumab has recently been introduced into the market in Hong Kong. Romosozumab is a monoclonal antibody that inhibits the protein sclerostin, which is an antagonist of the anabolic Wnt/β-catenin signalling pathway. Indeed, romosozumab confers dual action, promoting bone formation and inhibiting bone resorption at the same time, leading to a wider anabolic window than teriparatide. A head-to-head comparison trial showed that monthly subcutaneous injection of romosozumab led to a significantly higher bone mass gain at both spine and hip than teriparatide. Notably, in view of the need for balancing the risks and benefits, teriparatide and romosozumab can only be used for two years and one year respectively. After that, transition to anti-resorptive agents is recommended to extend the beneficial effect of anabolic agents on bone.

In 2013, the OSHK published a clinical guideline of osteoporosis treatment, which was the first risk-based treatment recommendation in the world. Now that the new anabolic agent romosozumab is available in the market, OSHK will likely update the clinical guideline. In the presence of different choices of anti-osteoporosis agents for different needs, pharmacological intervention remains the most effective strategy in improving bone mass and reducing fracture risk.

Table 1. Anti-osteoporosis agents available in Hong Kong (modified from the literature 12)

<table>
<thead>
<tr>
<th>Anti-resorptive agents</th>
<th>Denosumab</th>
<th>Calcitonin</th>
<th>Hormone replacement therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anabolic agents</td>
<td>Teriparatide</td>
<td>Denosumab</td>
<td>Romosozumab</td>
</tr>
<tr>
<td>Uncoupling agent</td>
<td>Strontium ranelate*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Due to potential increased risk in adverse cardiac events, it is rarely in use now.

Table 2. Common non-pharmacological interventions for osteoporosis management (summarised from the literature 9)

<table>
<thead>
<tr>
<th>Adequate protein intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidance of excessive caffeine intake</td>
</tr>
<tr>
<td>Education and psychosocial support</td>
</tr>
<tr>
<td>Fall prevention</td>
</tr>
<tr>
<td>Maintaining sufficient circulating vitamin D levels</td>
</tr>
<tr>
<td>Muscle strengthening</td>
</tr>
<tr>
<td>Reduction of alcohol consumption</td>
</tr>
<tr>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Sufficient calcium intake (either via diet or supplementation)</td>
</tr>
<tr>
<td>Weight-bearing exercise</td>
</tr>
</tbody>
</table>

UPDATES ON NON-PHARMACOLOGICAL INTERVENTION: VITAMIN D, FALL PREVENTION, AND CAFFEINE INTAKE

Table 2 summarises non-pharmacological interventions for osteoporosis according to a systematic review of clinical practice guidelines. Most of these interventions are well known to healthcare professionals and the general public, but there are several points to note regarding calcium and vitamin D, fall prevention, and caffeine intake. Sufficient calcium intake and vitamin D levels, either through diet or sunlight exposure, are important in maintaining bone health. However, intake of calcium-rich and vitamin D-rich foods, including dairy products, are generally low in the Chinese population. Adding to the fact that many people do not have sufficient sunlight exposure, possibly due to lack of outdoor activity and/or use of sunscreen products, there is a high prevalence of vitamin D deficiency and insufficiency in the Hong Kong population. Thus, calcium and vitamin D supplements are commonly used to compensate for the deficiency. For people aged 70 or above, the Institute of Medicine recommends 800 IU of dietary allowance and 4,000 IU of tolerable upper intake levels of vitamin D. It is not uncommon that high-dose vitamin D is prescribed to correct its deficiency. However, a recent trial showed that high-dose vitamin D (4,000 IU and 10,000 IU per day) reduced bone mass and quality, probably through alteration of calcium metabolism, as opposed to the general belief that higher doses of vitamin D could lead to better bone health. Another trial showed that high-dose vitamin D (60,000 IU per month) increased the risk of falls. Prescription of high-dose vitamin D could be potentially unsafe, and may result in worsened bone health and higher risk of fall.

In terms of risk of fall, although fall prevention clinics or services are available in Hong Kong, incidence of falls has never abated. Our recent study evaluated the territory-wide secular trend of hospitalised falls from 2005 to 2018 and found that the incidence of falls among people aged 60 or above has been increasing from 11.55 per 1000 person-years in 2005 to 15.24 per 1,000 person-years in 2018, resulting in an average annual percentage change of +2.3% (95% CI: +1.8% to +2.8%). Similarly, the incidence of fall-related severe injuries has also been increasing. Since fall-related injuries include fracture and other severe consequences such as intracranial bleeding and spinal cord injury, an effective and strategic fall prevention programme should be developed and implemented in our community to avert fall-related fracture and other related injuries.

Caffeine intake has long been known to increase calcium excretion, thus potentially increasing calcium loss and negative calcium balance. Coffee is one of the most consumed caffeine-rich beverages. Although it was reported that coffee intake was inversely associated with BMD, studies were reported in non-Asian population. Our recent study using data from more than 7,000 participants from the HKOS showed that habitual coffee intake was indeed positively associated
with lower BMD at both spine and hip. The similar positive association between coffee intake and BMD loss was also reported in Korea. Thus, excessive caffeine intake should be avoided; but habitual coffee intake, in appropriate amounts, may lead to better bone health.

**CONCLUSION**

In conclusion, osteoporosis and its associated fracture remain a huge public health issue in Hong Kong, and primary prevention plays a key role in fracture prevention. Using new tools to screen people at high risk of osteoporosis and fracture may allow earlier case identification and appropriate and timely pharmacological and non-pharmacological interventions, which in turn may subsequently reduce the burden of osteoporosis.

**References**

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MCHK CME Programme Self-assessment Questions

Please read the article entitled “Primary Prevention of Osteoporosis in Hong Kong: A Brief Update” by Dr Ching-lung CHEUNG and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 October 2021. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. Osteoporosis can be asymptomatic.
2. Fracture prediction tools are available.
3. Adherence to oral alendronate is well-documented to be poor.
4. Denosumab is an anabolic agent.
5. Romozosumab can increase bone formation and reduce bone resorption at the same time.
6. Romozosumab’s beneficial effect disappears quickly upon stopping treatment.
7. There is a clinical management guideline on osteoporosis specific for Hong Kong.
8. High-dose vitamin D (>4000 IU/day) is good for bone health.
9. Incidence of hospitalised falls has been decreasing in Hong Kong.
10. Habitual coffee intake, even not in excess, is detrimental to bone health.

Primary Prevention of Osteoporosis in Hong Kong: A Brief Update

Dr Ching-lung CHEUNG

Associate Professor
Department of Pharmacology and Pharmacy, the University of Hong Kong, Pokfulam, Hong Kong

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Answers to September 2021 Issue

Diabetes Mellitus - Who to Screen and What to Monitor for Renal Complications

Sodium Glucose Co-transporter 2 Inhibitors:
Glucose Lowering and Beyond

Dr Elaine CHOW
MBChB, PhD, MRCP(UK), FHKAM
Clinical Assistant Professor, Department of Medicine and Therapeutics
Division of Clinical Pharmacology, The Chinese University of Hong Kong

INTRODUCTION

Sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors) have been regarded as a game changer in the landscape of newer glucose-lowering drugs (GLDs), demonstrating significant improvements in hard cardiovascular (CV) endpoints where other GLDs have been neutral. A series of landmark cardiovascular outcome trials have shown SGLT2 inhibitors are associated with consistent reductions in CV death and heart failure hospitalisation, progression of chronic kidney disease (CKD) in patients with type 2 diabetes (T2D). The cardiorenal benefits of SGLT2 inhibitors extend beyond the diabetic population, showing a similar reduction in heart failure and CKD in non-diabetic individuals. SGLT2 inhibitors promote weight loss, lowers blood pressure with low hypoglycaemic potential but are associated with risks of genitourinary infection and euglycaemic diabetic ketoacidosis (DKA). In this review, we shall summarise the latest evidence for the use of SGLT2 inhibitors in diabetic and non-diabetic populations for cardio-renoprotection and beyond.

ACTIONS OF SGLT2 INHIBITORS

SGLT2 inhibitors, also known as the gliflozins, primarily act on the SGLT2 in the proximal tube of the kidney where 97% of filtered glucose is reabsorbed under normoglycaemic conditions. SGLT2 inhibition promotes glycosuria and excretion of glucose load. When compared with placebo, SGLT2 inhibitors are associated with a reduction in HbA1c by 0.6-0.9% regardless of background therapy.1 The degree of reduction in plasma glucose is proportionate to the ambient glucose concentrations and the rate of glomerular filtration. One of the advantages of SGLT2 inhibition is that its glucose-lowering actions occur independently of insulin and is thus associated with a low risk of hypoglycemia. Due to its glycosuric effects, SGLT2 inhibitors can promote negative energy balance and weight loss. Most studies report 2-3 kg weight loss in the initial six months of treatment which then stabilises.3 SGLT2 inhibitors also reduce plasma volume. The use of SGLT2 inhibitors are generally associated with a decrease in systolic and diastolic blood pressure by 4-6 mmHg and 1-2 mmHg, respectively (Fig. 1).

SGLT2 INHIBITORS AND CARDIOVASCULAR OUTCOMES IN TYPE 2 DIABETES

Although originally developed as a glucose-lowering agent, rather unexpectedly, SGLT2 inhibitors significantly improve cardiovascular-renal outcomes in type 2 diabetes in randomised controlled studies. In the Empagliflozin, Cardiovascular Outcome Event trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME 2 empagliflozin was associated with a significantly lower risk of major adverse cardiac events (MACE) (hazard ratio HR 0.6 [95% CI 0.74-0.99, p =0.04]) as compared with placebo in diabetes patients with established CVD.2-3 This was mainly driven by a 38% reduction in CV death. Hospitalisation for heart failure was also reduced by 35%. The Canagliflozin Cardiovascular Assessment Study (CANVAS) study, which recruited type 2 diabetes patients at high CV risk, including those without established CVD, also demonstrated a reduction in MACE and hospitalisation for heart failure HR 0.67 [95% CI 0.52, 0.87].4 The Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) trial which compared dapagliflozin versus placebo in individuals generally of lower CV risk also found a lower risk of hospitalisation for heart failure.

Fig. 1 Actions of sodium glucose cotransporter 2 inhibitors
SGLT2 inhibitors have pleiotropic effects. Glycosuric actions will reduce body weight. SGLT2 inhibitors activate tubuloglomerular feedback and have been shown to reduce hyperfiltration and intraglomerular pressure in the kidneys. These mechanisms may prevent kidney disease progression. It also reduces the total body sodium and water, reducing blood pressure, inhibiting sodium-hydrogen exchanger (NHE1) in the heart and kidneys. Additionally, SGLT2 inhibitors can increase lipolysis, favour ketone body formation which can improve substrate utilisation in the heart. Adapted from20
failure but no difference in MACE.5 (Fig. 2) Real-world evidence also supports the findings from randomised controlled trials. The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 Inhibitors (CVD-REAL 2) study compared outcomes of patients initiated on SGLT2 inhibitors versus other GLDs in six countries in the Asia Pacific, the Middle East and North America regions. The use of SGLT2 inhibitors was associated with a 50% lower risk of death and 40% lower risk of hospitalisation for heart failure.6

In the Dapagliflozin and prevention of Adverse outcomes in chronic kidney disease (DAPA-CKD) trial, which included 4304 patients with or without diabetes, dapagliflozin was associated with a lower risk of composite renal endpoint of ≥50% eGFR decline, kidney failure or death (HR 0.61 95% CI 0.52-0.72, p<0.001).9 Notably, the DAPA-CKD trial included patients with eGFR down to 25 ml/min/1.73m² which confirms the safety and efficacy of SGLT2i in advanced CKD. A summary of these trials is shown in Fig. 2.

### USE OF SGLT2 INHIBITORS IN NON-DIABETIC POPULATIONS

#### Non-diabetic Heart Failure

The observed differences in heart failure and survival occurred within months of SGLT2 inhibitor initiation and were largely independent of glucose-lowering effects. The exact mechanism by which SGLT2 inhibitors improve heart failure outcomes remains unclear, although changes in haemodynamic effects, osmotic diuresis, changes in cardiac substrate utilisation have been postulated as possible explanations.10,11 The role SGLT2 inhibitor use in heart failure patients without diabetes has been evaluated. The Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure (DAPA-HF) trial recruited 4744 patients with reduced ejection fraction, including 50% of the participants who did not have diabetes at baseline. In this study, similar reductions in heart failure hospitalisation and mortality were observed in individuals with and without diabetes.12 In another trial which compared empagliflozin versus placebo in heart failure patients with reduced ejection fraction, cardiovascular death or hospitalisation due to worsening heart failure was reduced by 25% in the empagliflozin group.13 Again, the magnitude of reduction was similar in those with and without diabetes.

#### Non-diabetic CKD

Glomerular hyperfiltration is not unique to the diabetic state and occur in other causes of CKD. Patients with CKD have reduced nephron mass. The single nephron may undergo structural hypertrophy leading to single nephron hyperfiltration.1 In the DAPA-CKD trial which included non-diabetic CKD patients, the relative risk reduction for the primary composite renal outcome with dapagliflozin was consistent in participants with type 2 diabetes (hazard ratio [HR] 0.64, 95% CI 0.52-0.79) and those without diabetes (0.50, 0.35-0.72). Consistent benefits of dapagliflozin were observed in patients with glomerulonephritides, ischemic or hypertensive CKD or secondary to unknown causes.14

#### Non-alcoholic Fatty Liver Disease (NAFLD)

Another emerging area is the use of SGLT2 inhibitors in NAFLD. NAFLD is common among individuals with T2D and is associated with the development of hepatic steatosis and non-alcoholic steatohepatitis (NASH). SGLT2 inhibitors have been shown to reduce liver fat14 in rodent models.15,16 Greater reductions in alanine...
A Comprehensive Osteoporosis Portfolio for Patients with Different Fracture Risks

Build Bone First

• "Dual-Action" with both anabolic & anti-resorptive effects
• Superior BMD improvement vs teriparatide within 1 year
• Continuous BMD improvement after transitioning to anti-resorptive after 1 year treatment course

Recommended for Very High Fracture Risk patients, e.g. those with recent fractures or T-score <−2.5

Relentless Protection

• Anti-resorptive with proven long-term effect
• Better BMD improvement vs bisphosphonates in both treatment-naive and bisphosphonate-treated patients
• Continuous BMD improvement with consistent safety profile proven with 10-year long-term clinical evidence

Recommended for High to Very High Fracture Risk patients, e.g. those with fracture history or T-score <−2.5
transaminase (ALT) in empagliflozin treated patients were in the EMPAREG OUTCOME trial, independent of weight and HbA1c reduction. Several studies have since investigated the effect of SGLT2i use on liver fat and fibrosis. In a small study of 50 type 2 patients with NAFLD, liver fat as detected by magnetic resonance imaging decreased from 16% to 11% treated among patients treated empagliflozin after 20 weeks.

ADVERSE EFFECTS OF SGLT2 INHIBITORS

The most common side effect of SGLT2 inhibitors are genitourinary infections due to increased glycosuria. Uncomplicated infections uncomplicated infections can mostly be managed routinely. Postural hypotension and volume depletion may also occur. A higher risk of lower-extremity amputation has been reported in the CANVAS programme among those receiving canagliflozin, as compared with placebo (HR 1.97, 95% CI 1.41, 2.75). However, this has not been reported with other SGLT2 inhibitors. Patients treated with SGLT2 inhibitors are at increased risk of diabetic ketoacidosis (DKA) which can occur within the euglycaemic range. Stress and starvation may tip the balance towards ketone production, especially in patients with relative insulin deficiency, while the glycosuric effects of SGLT2 inhibitors continue to keep glucose in an apparently normal range. In the CANVAS study, the risk of DKA was two-fold higher in the canagliflozin treated arm as compared with placebo (0.6 versus 0.3 per 1000 patient-years, HR 2.33 95% CI 0.76, 7.17). For these reasons, SGLT2 inhibitors should be discontinued during acute illness and at least 48 hours before operative procedures. Patients should be appropriately advised on these precautions.

CONCLUSION

The latest international guidelines recommend SGLT2 along with glucagon-like peptide-1 receptor agonists after first-line metformin therapy in type 2 diabetes patients at high atherosclerotic CVD risk, CKD or with heart failure. The role of SGLT2 inhibitor as an organ-protective drug for type 2 diabetes is established and supported by trial and real-world evidence. SGLT2 inhibitors will increasingly be used beyond their original glucose lowering indication. We anticipate cardiology and nephrology communities to be adopting these therapies to benefit a wider range of heart failure and CKD patients with and without diabetes in the future.

References

COVID-19 Vaccine Allergy Safety in Hong Kong

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Dr Philip H LI
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BACKGROUND

Coronavirus disease 2019 (COVID-19) has been responsible for the deaths of more than 4 million individuals and has caused irreparable damage to the society. Achieving herd immunity is currently the most promising anti-COVID-19 strategy to finally instigate the end of the pandemic. Since February 2021, Hong Kong has run a territory-wide COVID-19 vaccination programme, providing her residents with two vaccines the Sinovac CoronaVac and the Fosun Pharma BioNTech Comirnaty.

Despite the generally proven safety of the vaccinations, the overall vaccine acceptance rate was below 40% even before the commencement of Hong Kong’s COVID-19 vaccination programme. This correlated with the perceived harm of COVID-19 vaccination, as well as the lack of trust in the healthcare system. Soon after the initial rollout, reports of suspected anaphylaxis and severe allergic reactions to the COVID-19 vaccination rapidly dominated news reports, creating major safety concerns and vaccine hesitancy. Worryingly, most reported cases seemed to occur following first dose COVID-19 vaccination and was thought to be due to allergy to excipients found in mRNA vaccines (such as polyethylene glycol [PEG] found in Fosun Pharma BioNTech Comirnaty).

LOCAL RECOMMENDATIONS FOR COVID-19 VACCINE ALLERGY SAFETY

In response to concerns regarding COVID-19 vaccine allergy safety (VAS), the Hong Kong Institute of Allergy (HKIA) issued its first set of consensus statements on the approach of COVID-19 VAS in April 2021. With accumulation of both local and international experience regarding COVID-19 VAS, this was superseded by an updated consensus statements published in September 2021. The objectives of the statements were to define those people at higher risk of potential COVID-19 vaccine-associated allergies, and to highlight the importance of pre-vaccination and post-vaccination assessment by frontline healthcare workers and evaluation by specialists (Fig. 1). Both the original and updated consensus statements have also been adopted by the Department of Health. Individuals deemed to be at higher risk of COVID-19 vaccine-associated allergic reactions were recommended to defer COVID-19 vaccination until physician assessment, and, if deemed necessary, they can be referred for formal Allergist assessment to exclude potential COVID-19 vaccine or excipient-associated allergies.

Fig. 1: Updated Consensus Statements on COVID-19 Vaccine Allergy Safety in Hong Kong (Adopted from 4)

BALANCE BETWEEN VACCINE SAFETY AND UPTAKE

The HKIA VAS consensus statements proved to be successful in maintaining a low rate of COVID-19 vaccine-associated allergies in Hong Kong. As of Aug 2021, there have only been four confirmed cases of anaphylaxis (fewer than 0.5 cases per million doses
administered), which is much lower than incidences recorded in other countries\(^6\). However, there remains a balance between maintaining vaccine safety and promoting vaccine uptake.

To tackle the issue of COVID-19 VAS, the University of Hong Kong (HKU) and the Hospital Authority Hong Kong West Cluster (HKWC) have set up a dedicated VAS Clinic since March 2021. Specialists in the private sector have also set up dedicated services for COVID-19 vaccine allergy testing. However, with a shortage of Specialists in Immunology & Allergy in Hong Kong, it has been an overwhelming challenge to see and assess all referred patients in time, resulting in long waiting times and delays in vaccinations\(^10\). At the time of writing, the HKU/HKWC VAS Clinic runs at least three times per week but has received more than 2,500 new referrals in June 2021 alone. The waiting time for an appointment at VAS Clinic reached more than 7 years and led to a surge in public dissatisfaction. In response to this, the Hospital Authority established 7 new inter-disciplinary VAS Clinics across Hong Kong under its new “Hub-and-Spoke” allergy service model. Each of the 7 geographical territories under the Hospital Authority (clusters) had 1 “spoke” VAS Clinic, supported by the HKU/HKWC Immunology & Allergy team acting as the "Hub".

**INAPPROPRIATE REFFERALS, INACCURATE DIAGNOSES AND URGENT NEED TO STRENGTHEN ALLERGY SERVICES IN PRIMARY CARE**

The HKU/HKWC VAS Clinic received a total of 3,940 referrals between March to June 2021, but fewer than 15% of these patients have been seen due to limitations of manpower. In order to help shorten the waiting time, a protocol-based pre-consultation assessment has been instigated to help triage patients before attending the VAS Clinic. Worryingly, up to 45% of referrals were identified as inappropriate due to insufficient information or incorrect indications for referral (i.e., did not meet HKIA criteria for COVID-19 VAS evaluation). Furthermore, out of more than 180 patients who were referred for the history of suspected “anaphylaxis” (a precaution listed in the first version of the HKIA consensus statements\(^3\)), only 44% of them were found to actually fulfill anaphylaxis diagnostic criteria (i.e., 56% of patients diagnosed with “anaphylaxis” by their referring doctors were incorrectly diagnosed). If we extrapolate inappropriate referrals and incorrect diagnoses of anaphylaxis alone, we could easily have directed more than half of all patients to vaccination without the need for prior Allergist evaluation!

The success of the COVID-19 vaccination programme will rely on all our medical professionals, and this step of risk-stratification and prevention of unnecessary delays in vaccination heavily depends on the physicians initially evaluating a patient’s allergy history. In the vast majority of cases, primary care and family physicians should be able to make the appropriate judgment call based on objective clinical criteria provided by the HKIA recommendations. There is a dire need for further interdisciplinary collaboration and strengthening of Allergy services in primary care.

**MORE THAN 97% OF HIGH RISK PATIENTS PROCEED WITH COVID-19 VACCINATION AFTER EVALUATION**

In our experience, even among patients who were deemed at higher risk of COVID-19 vaccine-associated allergic reactions, only 2.4% of these patients were advised to defer COVID-19 vaccination following Allergist review (Fig. 2). The remaining patients were recommended to proceed with COVID-19 vaccination. Post-consultation telephone interviews confirm that around 80% of patients followed our advice and were vaccinated uneventfully, but around 20% have yet to book their vaccinations.

**URGENT CALL FOR PHARMACEUTICAL LEGISLATION REFORM**

Out of the 2.4% of patients advised to have their vaccination deferred, the majority had potential excipient allergies that could not be excluded. Currently, registered drugs in Hong Kong are still not mandated to include excipient lists in product inserts. Therefore, without being able to identify culprit excipients, excipient allergies remain almost impossible to diagnose, and some patients cannot be confidently deemed safe for vaccination. In response to this, the HKIA Updated Consensus Statements on the Approach to COVID-19 Vaccine Allergy Safety in Hong Kong now advocate administration of non-PEG containing vaccines for patients with possible excipient allergies.

However, this approach is far from ideal. We echo the HKIA consensus statements and implore that full excipient lists for all registered drugs should be mandated in Hong Kong as soon as possible\(^1\). In the interim, at least a comprehensive list of drug formulations containing excipients shared by the COVID-19 vaccines should also be made readily accessible for cross-referencing for physicians.
CONCLUSION

Achieving herd immunity in Hong Kong should be made an urgent priority. It is imperative that patients should not be inappropriately excluded from vaccination but equally important that the public maintains confidence in vaccination safety. Appropriate VAS guidance is essential to maintain low anaphylaxis rates, and yet such guidance should not become a barrier to vaccination uptake. Barriers to VAS include a high proportion of inappropriate referrals, inaccurate diagnosis of anaphylaxis, and inability to diagnose excipient allergies. Closer collaboration between primary care doctors and Allergy specialists should be fostered. Furthermore, relevant changes in pharmaceutical legislation should be made a priority to promote drug and vaccine allergy safety.

References
Repatha® has demonstrated consistent safety over a 5-year treatment period.

Safety and tolerability outcomes in the 5-year OSLER-1 study:

- Safety profile comparable to placebo
- No neutralizing antibodies detected

Repatha® is supported by well-established worldwide clinical experience.

Since launch, >660,000 patients have benefited from the sustained efficacy and consistent safety of Repatha®, including >41,000 patients in clinical trials.

Lowering LDL-C with Repatha® offers increased CV risk benefit over time.

Reductions in the key composite endpoint of CV death, MI or stroke in the FOURIER study:

In the first year (0–12 months)

Beyond the first year (12–36 months)

25%

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Safe Use of Chemical Restraint for Agitated and Violent Adult Patients

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INTRODUCTION
Agitation and aggression are common reasons for hospital attendance with escorts by law enforcement officers. Intoxications, psychosis, behavioural and psychological symptoms of dementia, traumatic brain injury, and medical problems (such as hypoglycaemia, electrolyte disturbance, sepsis, intractable pain, and acute urinary retention) are common correlations. They impose threats to the physical, psychological, and emotional wellbeing of the patient and attending staff.

BURDEN OF WORKPLACE VIOLENCE IN HEALTHCARE SETTINGS
In Hong Kong, healthcare workers frequently reported to the police for workplace violence, second to police officers. Among 400 to 500 reported cases of workplace violence in public health facilities annually, 22.1% involved threats, intimidation or aggressive behaviours, and 16.4% involved physical assault. More than 350 healthcare workers sustained physical and non-physical injuries. The three commonest medical specialities were Psychiatry units, Emergency departments, and Internal Medicine units. Nurses were the most vulnerable. While observing human rights and patient’s best interests, the healthcare team should take on emergency behavioural management in order to protect the patient and the staff, and to avoid interruption of important treatment. Emergency behavioural management conventionally adopts a stepwise approach, from de-escalating “talk-down”, seclusion in a quiet room in dim lighting, to the use of physical and chemical restraints.

EXCITED DELIRIUM IS A MEDICAL EMERGENCY
Excited delirium with intense mental and physiological excitement is a medical emergency, and is characterised by extreme agitation, hyperthermia, hostility, exceptional strength, and endurance without apparent fatigue. It carries a mortality of 8.3 - 16.5%, notably acute myocardial infarction, which demands high diagnostic vigilance and time-sensitive medical intervention. Proposed mechanisms of sudden death include dopaminergic overdrive, autonomic dysregulation, hyperthermia, rhabdomyolysis, cardiac arrhythmia, and impaired respiratory mechanics. The underlying causes are myriad and possibly time-consuming to identify. Non-pharmacological interventions are often inadequate. Chemical restraint is the reasonable next step to mitigate dopaminergic overdrive and circumvent metabolic acidosis.

CHEMICAL RESTRAINT – WHAT IS IT AND WHY BOTHER?
Chemical restraint is a pharmacological intervention to moderate patient behaviour, by transiently restricting freedom of movement. It is used in an emergency when confronted with an imminent risk of violence, especially involving weapons. It is just a means to an end – to buy time for safe physical assessments and investigations (e.g. blood and urine sampling, lumbar puncture, computed tomography scan of the brain), or to continue supportive care while awaiting wearing off of a stimulant medication.

This article focuses on the use of chemical restraint for adult patients who are not well known to the clinicians in healthcare settings. It is recognised that psychiatrists have more experience in managing patients with psychiatric conditions, and they may choose agents for chemical sedation other than those described below.

SAFE PRACTICE OF PHYSICAL AND CHEMICAL RESTRAINTS
Decision on and application of restraint is a shared-care process involving both doctors and nurses. On some occasions, physical restraints are decided on and applied as a nurse-initiated intervention out of urgency. Soon afterwards, doctors should be called in to assess in person and to consider chemical restraint in tandem. Applying restraint is often perceived as an infringement of personal freedom. Therefore, reasons for such orders should be documented clearly in the medical notes, instead of “restrain prn”. The need for restraint should be explained to patient and relatives, preferably supplemented by a fact sheet.

ISOLATED USE OF PHYSICAL RESTRAINTS IS NOT IDEAL
Healthcare providers are often tempted to apply physical restraint upfront to restrict patient movements. However, it may cause false reassurance to the treating
team that the problem has been solved instead of addressing the underlying pathology. The deleterious effects of physical restraints include falls, injuries, incontinence, circulation impairment, agitation, social isolation, and death. Patients with excited delirium may exhibit superhuman strength and appear impervious to pain. Struggling against physical restraints in a state of pain unawareness may cause excessive stress to musculoskeletal structures. It is associated with fracture, dislocation, rhabdomyolysis, strangulation, aspiration, asphyxiation, respiratory arrest, and death.

PROS AND CONS OF CHEMICAL RESTRAINT

Under proper administration and monitoring, the addition of a chemical restraint to an agitated patient offers a few advantages. Chemical restraint improves patient comfort by anxiolysis while buying time for laboratory results and wear-offs from toxic substances (e.g. stimulants). It may obviate the need for, or reduce the intensity of, physical restraints.

Chemical restraint may sometimes paradoxically worsen delirium, in particular for the elderly receiving benzodiazepine, and children receiving ketamine. Drug accumulation secondary to reduced clearance may cause inadvertent over-sedation or other toxic effects. Clinicians should aim to calm rather than to sedate acutely agitated patients. The ultimate goal is to restore self-control capacity, by reducing hyperarousal as rapidly and safely as possible.

PATIENT-BASED APPROACH TO CHEMICAL RESTRAINT

It is pivotal to rapidly identify and correct the readily treatable causes of agitation and aggression. All patients should be rapidly screened for hypoglycaemia, electrolyte imbalance, acute urinary retention, and traumatic brain injury. An efficient approach is to start initial treatment and address the provisional diagnosis at the same time. The selection of pharmacological agents and route of administration should be based on balancing risks and benefits in the patient’s context (Tables 1 and 2). Intramuscular benzodiazepines or olanzapine are the preferred initial agents for the treatment of acute undifferentiated agitation. Benzodiazepines are preferred to other antiepileptics for drug-induced seizure. Olanzapine and haloperidol can treat hallucinations related to acute psychosis. Ancillary therapies should be considered for specific conditions (Table 3).

<table>
<thead>
<tr>
<th>Route</th>
<th>When</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Alert</td>
<td>Non-invasive</td>
<td>Low oral bioavailability (15-27% for midazolam), Onset of action dependent on gastric emptying, absorption, first-pass effect</td>
</tr>
<tr>
<td>Rectal (mostly diazepam)</td>
<td>Drug-induced seizure</td>
<td>Does not require IV catheterisation</td>
<td>Erratic drug absorption, Less predictable dose-response relationship, Rectal perforation</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>Prehospital</td>
<td>Does not require IV catheterisation which can be difficult in an uncooperative patient</td>
<td>May be perceived as assault and not welcomed</td>
</tr>
<tr>
<td>Intravenous (peripheral line at first)</td>
<td>Route of choice for most in-hospital settings (emergency departments, wards, psychiatric units)</td>
<td>Rapid onset (~20 sec arm-to-brain circulation time)</td>
<td>May be perceived as assault and not welcomed, Difficult to establish IV access when violent, Heparin lock/catheter dislodgement, Thrombophlebitis, Bleeding, Pressure injury, Infusion pump necessary for sedative infusion</td>
</tr>
<tr>
<td>Inhalational</td>
<td>Post-operative (emergency agitation)</td>
<td>Rapid onset (&lt; 20 sec pulmonary circulation to brain time)</td>
<td>Cost</td>
</tr>
<tr>
<td>Intranasal (via atomiser)</td>
<td>Prehospital</td>
<td>Rapid onset (from 2 sec pulmonary circulation to brain time)</td>
<td>Atomiser is not widely available, Interference by nasal congestion and bleeding, In small volumes only, Mucosal damage</td>
</tr>
</tbody>
</table>

Table 1. Routes to administer sedatives

- Alert
- Patent airway
- Intact gag reflexes
- No vomiting
- Cooperative
- Drug-induced seizure
- Prehospital
- IV access is not available
- Young child
- Does not require IV catheterisation
- Avoids needlestick injury, especially while seizing
- Route of choice for most in-hospital settings (emergency departments, wards, psychiatric units)
- Uncooperative patient
- Rapid onset (~20 sec arm-to-brain circulation time)
- Titratable doses can be administered
- Repeated boluses
- Infusion with adjustable rates (e.g. midazolam, dexmedetomidine)
- Rapid onset (< 20 sec arm-to-brain circulation time)
- Short time to peak clinical effect
- Depth of sedation easily controllable
- Rapid offset (complete recovery after inhaling 100% oxygen for 3 - 5 min)
- No needles
- Prehospital
- Procedural sedation (e.g. close reduction of joint after seizure)
- Rapid onset
- Avoids needles
- Non-invasive
- Technically easy to administer
- No first-pass effect
- Digital monitoring
- Occasional device discomfort
- Difficult to establish IV access when violent
- Heparin lock/catheter dislodgement
- Thrombophlebitis
- Bleeding
- Pressure injury
- Infusion pump necessary for sedative infusion
- Easily overshoot
- Cost
- Space occupying, fixed equipment
- Cannot be used in uncooperative patients
- Leakage of gas causes occupational hazard
- Expertise not available in emergency department, Psychiatric units, general wards

- Oral
- Mucosal
- Atomiser
- No first-pass effect
- Easy to administer
- Briggs
- In small volumes only
- Mucosal damage
Robust and Consistent Efficacy Across PsA Domains

The first and only IL-17A inhibitor to demonstrate superiority in a head-to-head trial against adalimumab in PsA

SPIRIT H2H (BIOLOGIC NÄIVE): PERCENTAGE OF PATIENTS SIMULTANEOUSLY ACHIEVING

ACR 50 AND PASI 100 At WEEK 24, NRI

- Adalimumab (N=283)
- Taltz (N=283)

* P<0.01 vs adalimumab at week 8. Onset of response was statistically significant higher as early as week 8 through to week 24.
† P<0.05 vs adalimumab at week 24.
All patients had BSA ≥3%; patients with BSA ≥10%, PASI ≥12, sPGA ≥3 followed the approved dosing for moderate to severe plaque psoriasis.
ACR50 = American College of Rheumatology response criteria with 50% improvement;
BSA = body surface area; IL = interleukin; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; sPGA = static Physician Global Assessment.


Taltz Abbreviated Prescribing Information
Indications: Plaque psoriasis - Taltz is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Psoriatic arthritis - Taltz, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies. Dosage: Plaque psoriasis - Recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks. Psoriatic arthritis - Recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) every 4 weeks thereafter. For psoriatic arthritis patients with concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis. No data are available in children and adolescent < 18 years and limited information in subjects ≥ 75 years. Contraindications: Serious hypersensitivity. Clinically important active infections. Special Precautions: Infections, hypersensitivity, inflammatory bowel disease, immunization, Pregnancy, breast-feeding, fertility. Adverse Reactions: Injection site reactions, upper respiratory tract infections, lymea infection, oropharyngeal pain, nausea.

Please see Important Safety Information in the full prescribing information. Please see Instructions for Use included with the device.

Eli Lilly Asia, Inc.
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311 Gloucester Road, Causeway Bay, Hong Kong.
Tel: 2572 0160
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### Table 2. Commonly used agents for chemical restraint

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Starting dose (for agitated adult patient)</th>
<th>Onset</th>
<th>Duration of action</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepine</strong></td>
<td>- Enhances binding of GABA to GABA&lt;sub&gt;A&lt;/sub&gt; receptors</td>
<td>2 - 5 mg IV; every 3 - 5 min; 5 - 10 mg IM</td>
<td>&lt; 5 min (IV);</td>
<td>30 - 80 min (IV)</td>
<td>- effective for motor agitation</td>
</tr>
<tr>
<td></td>
<td>- Increases frequency of chloride channel opening</td>
<td>5 - 15 min (IM)</td>
<td>1 - 2 h (IM)</td>
<td></td>
<td>- short acting</td>
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<td></td>
<td></td>
<td>- greater sedation</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>- commonly used as IV infusion</td>
</tr>
<tr>
<td>Midazolam</td>
<td></td>
<td>5 min (IV); 0.5 - 3 h (PO)</td>
<td>20 - 100 h</td>
<td></td>
<td>-  respiratory depression</td>
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<tr>
<td></td>
<td>- long acting</td>
<td></td>
<td></td>
<td></td>
<td>- excessive somnolence</td>
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<td></td>
<td>- better for withdrawals</td>
<td></td>
<td></td>
<td></td>
<td>- paradoxical disinhibition (uncommon)</td>
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<tr>
<td></td>
<td>- prolonged sedation</td>
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<td></td>
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<tr>
<td></td>
<td>- not for IM (erratic effect, rise in creatine kinase)</td>
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<td></td>
<td>- oil based, painful injection</td>
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<tr>
<td>Diazepam</td>
<td>2 - 4 mg IV/ IM; Every 10 - 30 min for IV</td>
<td>5 - 10 min (IV); 30 - 45 min (IM)</td>
<td>2 - 6 h</td>
<td></td>
<td>- preferred benzodiazepine</td>
</tr>
<tr>
<td></td>
<td>- preferred benzodiazepine</td>
<td></td>
<td></td>
<td></td>
<td>- complete and rapid IM absorption</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2.5 - 10 mg IM/ IV (IV)</td>
<td>15 - 60 min (IM)</td>
<td>12 - 48 h</td>
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<td>- Less sedating than benzodiazepine</td>
</tr>
<tr>
<td></td>
<td>- Less extrapyramidal symptoms</td>
<td></td>
<td></td>
<td></td>
<td>- IV route is off-label use by FDA standard</td>
</tr>
<tr>
<td></td>
<td>- Extrapyrarmidal effects (amendable to benztrpin IM, benzhexol PO)</td>
<td></td>
<td></td>
<td></td>
<td>- Neuroleptic malignant syndrome</td>
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<tr>
<td></td>
<td>- prolonged QT interval</td>
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<tr>
<td>Antipsychotic</td>
<td>- &quot;Typical&quot; antipsychotic</td>
<td>2.5 - 10 mg IM/ (IV)</td>
<td>15 - 45 min (IM)</td>
<td>Up to 24 h</td>
<td></td>
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<tr>
<td>Haloperidol</td>
<td>- Blocks dopamine D2 &amp; D3, histamine and noradrenaline receptors</td>
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<td></td>
<td></td>
<td>- Less extrapyramidal symptoms</td>
</tr>
<tr>
<td></td>
<td>- &quot;Atypical&quot; antipsychotic</td>
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<td></td>
<td>- Excessive sedation</td>
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<td></td>
<td>- Blocks 5-HT&lt;sub&gt;2&lt;/sub&gt;A, 5-HT&lt;sub&gt;2&lt;/sub&gt;C, histamine-I, muscarinic M1-5 receptors</td>
<td></td>
<td></td>
<td></td>
<td>- Reduced seizure threshold</td>
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<tr>
<td>Olanzapine</td>
<td>5 - 10 mg PO; 10 mg (IM)</td>
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<tr>
<td></td>
<td>- More rapid onset than antipsychotics</td>
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<td></td>
<td>- May not be adequate as a sole agent</td>
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<tr>
<td></td>
<td>- Extended duration of treatment for benzodiazepine</td>
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<td></td>
<td>- Reserved for combative, excited delirium</td>
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<tr>
<td></td>
<td>- Possible respiratory depression, hypotension (especially IM), bradycardia, syncope</td>
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<tr>
<td></td>
<td>(caution for those with significant medical comorbidities)</td>
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<tr>
<td>Phenylcide derivative</td>
<td>1 mg/kg (IV); 5 mg/kg (IM)</td>
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<tr>
<td>Ketamine</td>
<td>- Non-competitive NMDA receptor antagonist</td>
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<tr>
<td></td>
<td>- Centrally acting selective alpha-2 (subtypes A, B, C) agonist</td>
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<tr>
<td></td>
<td>- Sedative-analgesic with sympatholytic property</td>
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<tr>
<td></td>
<td>Loading: 1 mcg/kg IV over 10 min</td>
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<td></td>
<td>- Only licensed for up to 24 h of administration</td>
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<tr>
<td></td>
<td>Maintenance: 0.2 - 0.7 mcg/kg/h IV infusion (not longer than 24 h)</td>
<td></td>
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<td></td>
<td>- Advantage of preserved respiratory drive during sedation</td>
</tr>
<tr>
<td></td>
<td>- Only licensed for up to 24 h of administration</td>
<td></td>
<td></td>
<td></td>
<td>- Reduces blood pressure and heart rate for stimulant intoxications</td>
</tr>
<tr>
<td></td>
<td>- Advantages of preserved respiratory drive during sedation</td>
<td></td>
<td></td>
<td></td>
<td>- Candidate agent for switch therapy after high-dose benzodiazepines</td>
</tr>
<tr>
<td></td>
<td>- Reduces blood pressure and heart rate for stimulant intoxications</td>
<td></td>
<td></td>
<td></td>
<td>- Risks of hypotension, bradycardia, and sinus arrest (caution in advanced heart block and severe ventricular dysfunction)</td>
</tr>
<tr>
<td>Centrally acting alpha-2 adrenergic receptor agonist</td>
<td>- Centrally acting selecteive alpha-2 (subtypes A, B, C) agonist</td>
<td>Loading: 1 mcg/kg IV over 10 min</td>
<td>5 - 10 min</td>
<td>60 - 120 min</td>
<td>- Only licensed for up to 24 h of administration</td>
</tr>
<tr>
<td></td>
<td>- Sedative-analgesic with sympatholytic property</td>
<td>Maintenance: 0.2 - 0.7 mcg/kg/h IV infusion (not longer than 24 h)</td>
<td></td>
<td></td>
<td>- Advantage of preserved respiratory drive during sedation</td>
</tr>
<tr>
<td></td>
<td>- Candidate agent for switch therapy after high-dose benzodiazepines</td>
<td></td>
<td></td>
<td></td>
<td>- Reduces blood pressure and heart rate for stimulant intoxications</td>
</tr>
<tr>
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<td>- Risks of hypotension, bradycardia, and sinus arrest</td>
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<td>- Candidate agent for switch therapy after high-dose benzodiazepines</td>
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<td>(caution in advanced heart block and severe ventricular dysfunction)</td>
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</tbody>
</table>

GABA: gamma-aminobutyric acid; IV: intravenous; IM: intramuscular; PO: oral; NMDA: N-methyl-D-aspartate; FDA: United States Food and Drug Administration
POST-RESTRAINT MANAGEMENT

Close monitoring of patient is needed to ensure safety when restraints are in place. Standards of personal care, including personal hygiene, nutrition, hydration, continence, turning, as well as protection against aspiration and deep vein thrombosis, should be upheld. Monitoring of vital signs, oxygen saturation, cardiac rhythm, fluid inputs and outputs, circulation, and neuro-observation should continue. The duration of restraints should be minimal. Hospital or clinical department-based clinical guidelines should be in place, subject to regular audits and reviews.12,13

CONCLUSION

Despite ongoing controversy, chemical restraint is a clinically important intervention for timely protection against self-harm and workplace violence. It should be considered early when physical restraint is applied. The selection of pharmacological agents and administration routes should be based on the clinical condition. Patient safety and rights should command top priorities.

Table 3. Preferred therapies for specific conditions

<table>
<thead>
<tr>
<th>Xenobiotic/condition</th>
<th>Preferred therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute psychosis and mania</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Chronic alcoholism</td>
<td>Thiamine, dextrose</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Sodium nitrite &amp; sodium thiosulphate; or hydroxocobalamin</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Digoxin immune Fab (DigiFab®)</td>
</tr>
<tr>
<td>Drug-induced agitation (including Chinese medicine e.g. ma huang, ginseng, ephedra)</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Opiates</td>
<td>Naloxone</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>Dextrose, octreotide (for refractory hypoglycaemia)</td>
</tr>
<tr>
<td>Toxic alcohols (e.g. methanol)</td>
<td>Ethanol, fomepizole, haemodialysis</td>
</tr>
<tr>
<td>Valproate</td>
<td>L-carnitine</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>Benzodiazepines for benzodiazepine, zopiclone and alcohol withdrawals; Methadone for opiate withdrawal</td>
</tr>
<tr>
<td>Hyperthermia syndromes</td>
<td>Physostigmine (+/- benzodiazepine)</td>
</tr>
<tr>
<td>Anticholinergic delirium (e.g. scopolamine, Datura species)</td>
<td>Coolings, benzodiazepines, dantrolene</td>
</tr>
<tr>
<td>Malignant hyperthermia</td>
<td>Cooling, benzodiazepines, dantrolene</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome</td>
<td>Cooling, benzodiazepines, bromocriptine</td>
</tr>
<tr>
<td>Serotonin syndrome</td>
<td>Cooling, benzodiazepines, cyproheptadine</td>
</tr>
<tr>
<td>Sympathomimetic toxidrome</td>
<td>Benzodiazepines</td>
</tr>
</tbody>
</table>

Table 4. Common pitfalls during sedative administration

<table>
<thead>
<tr>
<th>Pitfalls</th>
<th>Suggested solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate tranquillisation</td>
<td>- Ensure adequate dosage</td>
</tr>
<tr>
<td></td>
<td>- Administer intravenous push bolus injections unless otherwise specified</td>
</tr>
<tr>
<td></td>
<td>- Ensure sufficient intravenous line flush volume after each bolus: at least 10 - 20 mL 0.9% sodium chloride solution</td>
</tr>
<tr>
<td></td>
<td>- Switching agents from one class to another, or combining more than one class of therapies</td>
</tr>
<tr>
<td>Fear of overshooting and under-sedation</td>
<td>Consider a stepwise approach of repeated boluses under close monitoring: Diazepam: 5 mg as the first bolus, followed by another 5 mg after 3 - 5 min, and then double the dose to 10 mg, as follows: 5 mg + 5 mg + 10 mg + 10 mg + 20 mg + 20 mg,... until desired response is achieved. The total dose of diazepam received to achieve the first successful sedation can be up to 50 - 100 mg in severe stimulant intoxications.</td>
</tr>
<tr>
<td>Forgot about other medical needs during chemical restraint</td>
<td>- Hypertension and tachycardia signal poor analgesia</td>
</tr>
<tr>
<td></td>
<td>- Bear in mind that not all sedatives have analgesic property</td>
</tr>
<tr>
<td></td>
<td>- Consider morphine/entanyl co-administration, especially for pain in withdrawal, delusional parasitosis in methamphetamine and cocaine intoxications</td>
</tr>
<tr>
<td></td>
<td>- Routine input/ output charting</td>
</tr>
<tr>
<td>Incomplete documentation</td>
<td>- Use standard forms and checklists with structured formats; a good example is a resuscitation form which documents serial vital signs and medications with dose, route, and time.</td>
</tr>
<tr>
<td></td>
<td>- Shared care team approach: endorsement by both nurses and doctors</td>
</tr>
<tr>
<td></td>
<td>- Cross-checking while logging the drugs administered, particularly for items regulated under Dangerous Drugs Ordinance (Cap. 134)</td>
</tr>
</tbody>
</table>

Certain patient groups deserve special attention because of altered pharmacokinetiics, pharmacodynamics, and risk of exposure to culprit agents. Elderly patients have more adipose tissue, such that the volumes of distribution and half-lives of lipophilic drugs increase. Slower renal clearance, reduced first-pass effect (increased oral bioavailability), and polypharmacy make elderly patients more prone to drug interactions and toxic effects. Chronic alcoholics are prone to thiamine deficiency and malnutrition. Bodybuilders may use androgenic-anabolic steroids, which could cause aggression. One should be cautious to avoid withdrawals when administering antidotes to patients with substance dependence, such as naloxone for opiates, and flumazenil for benzodiazepines. Chronic sedative users may require higher sedative doses during chemical restraint. Antipsychotics with the risk of prolonging QT interval should be avoided to sedate a patient on other QT-prolonging drugs. If possible, an electrocardiogram will be helpful to aid agent selection.
References

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</table>

**Zoom Lecture**
- In Search Of Completely Clear Skin – Findings On PASI 100 Results From Clinical Trials And Real Life In Plaque Psoriasis - Online
- The Hong Kong Neurosurgical Society Monthly Academic Meeting
- Nutrition Intervention for Type 2 Diabetes Mellitus (T2DM) Patients - Online

**Certificate Course on**
- Cardiology 2021 (Video Lectures)
- Optometric Practice from Infants to the Elderly (Video Lectures)
- Certificates on Respiratory Medicine 2021 (Video Lectures)
- Renal Medicine 2021 (Video Lectures)
- Optometric Practice from Infants to the Elderly (Video Lectures)

**Zoom Lecture**
- The Sweetspot for DM Management - What’s the Role of SGLT2 Inhibitor? - Online
- Updates on Menstrual Disorders Management - Hormonal Treatment and Myths - Online
- The Role of Novel Antidepressants in Managing Major Depressive Disorder (MDD) - Online
- The Latest Scientific Update - Online

**FMSHK Executive Committee Meeting**
- FMSHK Council Meeting

**Certificate Course on**
- Cardiology 2021 (Video Lectures)
- Cardiology 2021 (Video Lectures)
- Cardiology 2021 (Video Lectures)
- Cardiology 2021 (Video Lectures)
- Cardiology 2021 (Video Lectures)
- Cardiology 2021 (Video Lectures)
- Cardiology 2021 (Video Lectures)
- Cardiology 2021 (Video Lectures)
Certificate Course on
Communication and Swallowing Development and Disorders in Children 2021
(Video Lectures)

Jointly organised by
The Federation of Medical Societies of Hong Kong
The Hong Kong Association of Speech Therapists

Objectives: Upon completion of the course, participants will have a basic understanding towards the development of communication and swallowing in children, common communication and swallowing disorders, as well as basic components in assessing and treating communication and swallowing disorders. With the above knowledge, participants will be able to develop greater awareness in identifying children with suspected communication and swallowing disorders at their clinical practice or even in their own family.

<table>
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<tr>
<th>Date</th>
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<th>Speakers</th>
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<tr>
<td>9 November 2021</td>
<td>Early Language Development &amp; Disorders</td>
<td>Dr. Anita Wong (Associate Professor, BSc (Speech and Hearing Sciences), Faculty of Education, The University of Hong Kong)</td>
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<tr>
<td>16 November 2021</td>
<td>Speech Sound Development &amp; Disorders</td>
<td>Dr. Carol To (Associate Professor, Academic Unit of Human Communication, Development and Information Sciences, Faculty of Education, The University of Hong Kong)</td>
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<tr>
<td>23 November 2021</td>
<td>Dyslexia</td>
<td>Dr. Dustin Lau (Associate Professor, Department of Chinese &amp; Bilingual Studies, Hong Kong Polytechnic University)</td>
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<tr>
<td>30 November 2021</td>
<td>Bilingual Development in Children</td>
<td>Dr. Angel Chan (Associate Professor, Department of Chinese &amp; Bilingual Studies, Hong Kong Polytechnic University)</td>
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<tr>
<td>7 December 2021</td>
<td>Understanding Developmental Stuttering in Children</td>
<td>Dr. Thomas Law (Assistant Professor &amp; Deputy Chief of Division, Department of Otorhinolaryngology, Head and Neck Surgery, The Chinese University of Hong Kong)</td>
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<tr>
<td>14 December 2021</td>
<td>Aural Rehabilitation for Children with Hearing Impairment</td>
<td>Dr. Kathy Lee (Associate Professor &amp; Chief Division of Speech Therapy, Department of Otorhinolaryngology, Head and Neck Surgery, Faculty of Medicine, The Chinese University of Hong Kong)</td>
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Date: 9, 16, 23, 30 November & 7, 14 December 2021 (Every Tuesday)

Duration of session: 1.5 hours
Time: 7:00 pm – 8:30 pm

Course Feature: Video lectures (with Q&A platform for participants to post the questions)
Quiz for doctors: To tie in with the CME requirements for video lectures, DOCTORS are required to complete a quiz after the completion of each lecture

Language Media: Cantonese (Supplemented with English)
Course Fee: HK$1,000 (6 sessions)
Certificate: Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)
Enquiry: The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898  Fax: 2865 0345  Email: vienna.lam@fmshk.org

CME / CNE Accreditation in application
Online Application from website: http://www.fmshk.org
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<th>Function</th>
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<td>The Sweet Spot for DM Management: What’s the Role of SGLT2 Inhibitor? - Online</td>
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<td>Certificate course on Respiratory Medicine 2021 (Video Lectures)</td>
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<td>Updates on Menstrual Disorders Management: Hormonal Treatment and Myths - Online</td>
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<td>Certificate Course on Optometric Practice from Infants to the Elderly (Video Lectures)</td>
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<td>Speaker: Mr. Chan Ka Ho, Paco</td>
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<td>Update in Management of Lung Cancer - Online</td>
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<td>In Search Of Completely Clear Skin – Findings On PASI 100 Results From Clinical Trials &amp; Real Life In Plaque Psoriasis - Online</td>
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<td>Speaker: Dr Chan Kit</td>
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<td>The Role of Novel Antidepressants in Managing Major Depressive Disorder (MDD) - Online</td>
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<td>FMESHK Executive Committee Meeting</td>
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<td></td>
<td>Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wan chai, Hong Kong</td>
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<td>Speaker: Dr Ko Kwok Chun, Jason</td>
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<td>Nutrition Intervention for Type 2 Diabetes Mellitus (T2DM) Patients - Online</td>
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<td>Speaker: Dr Cheng Yue Hong</td>
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<td>Speaker: Dr CHAN Leung Kwai, Jason</td>
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Certificate Course on
Optometric Practice from Infants to the Elderly (Video Lectures)

Jointly organised by
The Federation of Medical Societies of Hong Kong
The Hong Kong Society of Professional Optometrists

Objectives:
To provide an overview of optometric care from infants to the elderly. After attending the course, attendees will learn how to deal with common vision disorders and refer patients to optometrists.

<table>
<thead>
<tr>
<th>Date</th>
<th>Topics</th>
<th>Speakers</th>
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<tbody>
<tr>
<td>13 October 2021</td>
<td>Paediatric Vision Development and Assessment</td>
<td>Mr. Chan Ka Ho, Paco MOptom, BSc (Hons) Optom</td>
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<tr>
<td>20 October 2021</td>
<td>Amblyopia, Binocular Vision Anomalies and Vision Training</td>
<td>Miss Bibianna Yu BSc(Hons)Optom, MPhil, FAAO</td>
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<tr>
<td>27 October 2021</td>
<td>Vision Rehabilitation of Low Vision Patients</td>
<td>Dr. Helen Eng OD FAAO</td>
</tr>
<tr>
<td>3 November 2021</td>
<td>The Latest Clinical Studies on Myopia Management for Children</td>
<td>Dr. Ng Sheung Shun, Vincent BSc (Hons) Optom, Ph.D, FAAO</td>
</tr>
<tr>
<td>10 November 2021</td>
<td>Optometric Care on High Myopia</td>
<td>Dr. Ng Sheung Shun, Vincent BSc (Hons) Optom, Ph.D, FAAO</td>
</tr>
<tr>
<td>17 November 2021</td>
<td>Specially Contact Lenses and Tips of Proper Contact lens Wear</td>
<td>Miss Yee Man Chi, Gigi MSc in Optometry, BSc (Hons) Optom, FBCLA</td>
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</table>

Date: 13, 20, 27 October & 3, 10, 17 November 2021 (Every Wednesday)
Duration of session: 1.5 hours (6 sessions)
Time: 7:00 pm – 8:30 pm
Course Feature: Video lectures (with Q&A platform for participants to post the questions)
Language Media: All lectures are conducted in Cantonese (except Lecture 3 is in English)
Quiz: Doctors and Optometrists are required to complete a quiz after the completion of each lecture
Course Fee: HK$1,000 (6 sessions)
Certificate: Awarded to participants with a minimum attendance of 70%
Deadline: 6 October 2021
Enquiry: The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898  Fax: 2865 0345  Email: vienna.lam@fmshk.org

CME and CNE Accreditation in application
9 CPD points for Optometrists for the whole course and the points will be awarded according to the number of hours attended
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Answers to Radiology Quiz

Answers:

1. Left MCA infarct. MCA supplies the lateral aspect of frontal, temporal and parietal lobes, the corona radiata, globus pallidus, caudate and putamen. There will be contralateral hemiparesis and hemisensory loss of the face, upper and lower extremities. If the dominant side is affected, there would be aphasia due to the involvement of Broca’s area, and Wernicke’s area.

2. CT cerebral angiogram.

3. Hemorrhagic transformation.


Dr Carol PY CHIEN
MBBS, FRCR
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References:
http://www.espen.org/ESPENguidelines.html

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**References:**

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