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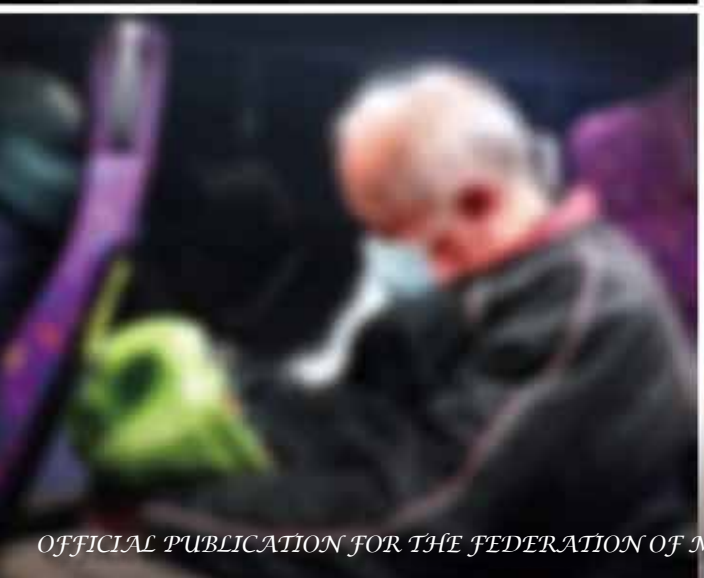
Sleep Medicine



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Onset of action from **5 minutes**[1]

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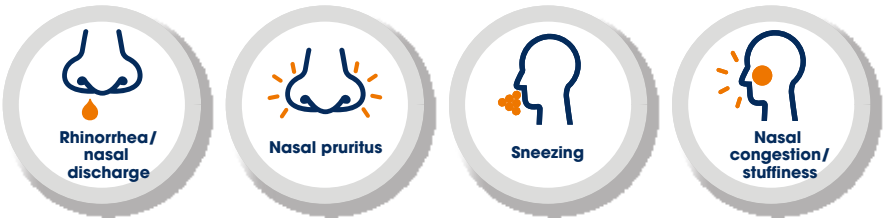

- Significant ocular symptom relief from **10 minutes**[1]

DYMISTA NASAL SPRAY SUMMARY OF PRODUCT INFORMATION
1. TRADE NAME: DYMISTA NASAL SPRAY **2. PRESENTATION:** Each Dymista nasal spray bottle contains 23 g suspension in 25 ml bottles. One actuation (0.14 g) delivers 137 micrograms azelastine hydrochloride (= 125 mcg azelastine) and 50 mcg fluticasone propionate. **3. INDICATIONS:** Relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient. **4. DOSAGE:** For nasal use only. Adult and adolescents (12 years and older): one actuation in each nostril twice daily (morning and evening). Paediatric population: not recommended for use in children below 12 years. Elderly population: no dose adjustment required. No data in patients with renal and hepatic impairment. **5. CONTRAINDICATIONS:** Hypersensitivity to the active substances or to any of the excipients. **6. WARNINGS & PRECAUTIONS:** Systemic effects may occur, particularly at high doses for prolonged periods. Potential systemic effect may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioral effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Caution is advised in patients with severe liver disease given the extensive first-pass metabolism of Dymista Nasal Spray and thus higher systemic exposure of intranasal fluticasone propionate. Reduce intranasal fluticasone formulation to the lowest dose at which effective control of symptoms is maintained. Weigh the possible benefit against risk in patients with tuberculosis, any type of untreated infection, or have had a recent surgical operation or injury to the nose or mouth. Care must be taken in patient transferring from systemic steroid treatment to Dymista Nasal Spray with impaired adrenal function. Closely monitor patients with a change in vision or with a history of increased ocular pressure, glaucoma and/or cataracts. Growth retardation has been reported in children. Regularly monitor the growth of adolescents receiving prolonged treatment with nasal corticosteroids. Dymista contains benzalkonium chloride, which may cause irritation of the nasal mucosa and bronchospasm. **7. INTERACTIONS:** Avoid concomitant use with ritonavir. Care is advised in concomitant potent CYP3A4 inhibitors (e.g. ketoconazole), and sedative or central nervous medication. **8. PREGNANCY AND LACTATION:** No or limited data in pregnant woman. Unknown if the ingredients/metabolites are excreted in human breast milk. Used only if the potential benefit justifies the potential risk. **9. SIDE EFFECTS:** Epistaxis. Headache, dysgeusia, unpleasant smell.
Reference: HK PI (JAN 2014) Date of preparation: MAR2021 Identifier number: DYMI0321

FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.

Reference: 1. Bousquet J, Meltzer EO, Couroux P, *et al.* Onset of Action of the Fixed Combination Intranasal Azelastine-Fluticasone Propionate in an Allergen Exposure Chamber. *J Allergy Clin Immunol. Pract.* 2018;6(5):1726–1732.

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The Cover Shot

No one can deny the healing power of deep sleep. Sleep deprivation is probably the reason why those who have missed their opportunities for a good night's sleep would be found catching their cat naps anywhere and at any time. The slogan for this year's World Sleep Day is "Regular Sleep, Healthy Future". This slogan serves well to remind us that regular and adequate sleep will lead to better physical and mental health. Conversely, when sleep fails, health will sooner or later decline. Let us not take nature's gift of healing for granted. May I wish all readers good health and blissful sleep!

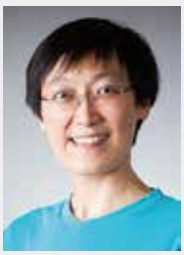
Description of the Photographer

Ms Liu was awarded the title of Photographic Society of America (PSA) Who's Who Top Ten in 2001 & 2002 as well as Artiste of The International Federation of Photographic Art (A.FIAP) in 2003 in International Salon of Photography.

She has been an Associate of The Royal Photographic Society of Great Britain (Visual Art Panel, A.RPS) since 2002.

Locally, she was awarded an Associate and Fellow of various local photographic societies in Hong Kong since 1993.

Over the years, she had taken up the positions of Vice-President, Salon Chairman and Salon Judge for several local photographic societies.



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Sleep Medicine from Development to Public Health

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Editor

Prof WING Yun-kwok

In this issue of the Hong Kong Medical Diary, we are offering a series of reviews on common and pertinent sleep problems, including obstructive sleep apnoea syndrome, insomnia, hypersomnia and parasomnia. The topics are written by specialists across different disciplines, from paediatricians, physicians, psychiatrist to research scientists. As reviewed by Dr KL Choo, past president of the Hong Kong Society of Sleep Medicine, Sleep Medicine is a new and young field of medicine.[1] The wide range of problems, trans-disciplinary nature and a multitude of health implications have served as the cornerstones for the rapid development of sleep medicine locally and internationally.

After all, everyone will need to sleep. The latest understanding of the breadth of functions of sleep includes metabolic waste clearance (glymphatics) of the brain, metabolism, immune modulation, memory consolidation, emotional regulation, growth and development. No wonder that sleep is closely related to physical and mental health, healthy development and future neurodegeneration. Yet, modern society has trivialised and under-valued the importance of sleep as a 'dispensable commodity' secondary to other more 'urgent' or 'priority' academic, occupational, and recreational activities. Sleep deprivation is commonly seen in all age groups, especially among Asians. A recent study using large scale wearables data suggested that East Asians were sleeping at least 30-40 minutes lesser and about 1-1.5 hours later than Oceanians across youth to elderly.[2] The more intriguing fact is that within the East Asian region, Hong Kong has the latest bedtime. This study echoes the findings of our recent comparison of the children between Hong Kong and Shanghai that Hong Kong children had a consistently later bedtime and wakeup time with shorter sleep duration than Shanghai children. Over the past ten years, the secular trend suggested a worrying picture that Hong Kong children decreased their sleep duration further from a mean of 9.2 hours to 8.87 hours, while Shanghai children gained from 9.39 hours to 9.56 hours.[3] Sleep deprivation in Hong Kong is an alarming and hidden 'epidemic'.

How often does a general doctor encounter sleep problems? Consistent data will suggest that about 1 in 5 patients attending a general clinic may suffer from insomnia. However, only 40% of adults with insomnia and 10% of youth with insomnia will seek medical help at all.[4] On the other hand, it is not uncommon among medical practitioners to ignore sleep problems. Perhaps, the historical development of insomnia and psychiatric illness may reveal the importance of a paradigm shift in tackling the sleep problem. It has long been assumed that insomnia is a secondary symptom of underlying psychiatric disorder such as depression. In other words, one would expect the improvement of insomnia/sleep problems upon resolution of depression. However, mounting evidence would suggest a far more complicated relationship in which insomnia and depression share a reciprocal and bidirectional relationship.[5] Thus, the latest evolution in our conceptual shift will consider insomnia as an independent comorbidity rather than a secondary symptom. Along with this paradigm shift in our approach to insomnia, the resultant proper recognition and treatment of comorbid insomnia has improved the depression outcome. The

comorbid concept has also provided a new direction of mental health prevention: by targeting insomnia, one may prevent depression in future.[6]

How should we approach sleep problems? Starting from basic history on sleep pattern (weekday-weekend), enquiry of sleep symptoms including insomnia, snoring, sleepwalking, nightmares and dream enactment, daytime sleepiness and functional assessment, one will readily make a clinical diagnosis of sleep problems. The use of standardised and validated questionnaires may aid the clinical assessment and monitoring of treatment responses. Some of the sleep disorders will need further sleep assessment, including polysomnography.

Sleep medicine has an obvious implication for our daily clinical practice and is a major but under-recognised public health issue. Healthy sleep should be everyone's concern.

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Parasomnia : an Update on Approach and Management

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 30 April 2021.

Parasomnia refers to a group of sleep conditions characterised by undesirable physical or physiological events. It embraces a variety of sleep disorders that clinicians may come across at routine clinical practice, such as sleepwalking and nightmares. Parasomnia also embraces conditions that warrant clinical attention because of sleep-related aggression and potential neurodegenerative implications, such as rapid eye movement (REM) sleep behaviour disorder (RBD).

According to the International Classification of Sleep Disorder, 3rd edition (ICSD-3)[1], parasomnias are classified according to the timing of the occurrence of abnormalities during sleep-wake transitions or different sleep stages, as in non-rapid eye movement (NREM) parasomnia and rapid eye movement (REM) parasomnia(Table 1). This paper will present a summary on the clinical approach to and management of some predominant movement-related NREM and REM parasomnias, namely the disorders of arousal (DOAs) under the category of NREM parasomnia, and REM sleep behaviour disorder (RBD) respectively.

Table 1. Parasomnias listed in ICSD-3 (Excerpted from the American Academy of Sleep Medicine; 2014 [1])

NREM-related parasomnias
• Disorders of arousal
• Confusional arousals
• Sleepwalking
• Sleep terror
• Sleep-related eating disorder
REM-related parasomnias
• REM sleep behaviour disorder
• Recurrent isolated sleep paralysis
• Nightmare disorder
Other parasomnias
• Exploring head syndrome
• Sleep-related hallucinations
• Sleep enuresis
• Parasomnia due to a medical disorder
• Parasomnia due to a medication or substance
• Parasomnia, unspecified
NREM: non-rapid eye movement; REM: rapid eye movement; ICSD-3: International Classification of Sleep Disorder, 3rd edition

DISORDERS OF AROUSAL

Classic examples of NREM parasomnias are confusional arousal, sleepwalking (somnambulism) and night terror. These three conditions are regarded as DOAs occurring during NREM stage 3 sleep, commonly known as deep/slow wave sleep, sharing the common feature of dissociation of awareness and behaviours. The individuals are usually unresponsive to the external environment, and their EEG shows a mixture of both sleep and wake features, suggesting a NREM sleep instability.[2-4] While most patients are typically amnesic, sleepwalkers may sometimes have a varying level of consciousness, ranging from complete amnesia, partial memory recollection to reports of dream-like activities. Brain imaging studies further confirm the dissociative nature of DOAs, particularly in sleepwalking.[5-6] Perfusion patterns during a sleepwalking episode by single-photon emission computed tomography (SPECT) showed simultaneous activation in the posterior cingulate cortex and the anterior cerebellum, but deactivation of the arousal system, namely, the frontoparietal associative cortices.[5] Similar neuroimaging findings of abnormal coexistence of local sleep and wake brain activities have been reported, and hence explaining the dissociation of behaviours and varying degrees of consciousness during DOAs.[6]

DOAs have diverse clinical manifestations[1], ranging from autonomic manifestations such as tachycardia and sweating in night terror, simple ambulatory behaviours, to more complex elaborate behaviours such as driving, sexual behaviours and aggression. The clinical characteristics and demographics of confusional arousals, sleepwalking and night terror are listed in Table 2. Instead of a distinct entity, these three NREM parasomnias may co-exist and appear as a continuum most commonly seen in children.[7] While confusional arousals usually happen in infants and toddlers, night terror is more common among preschoolers, and sleepwalking is more commonly found in older children.[7]

The etiologies of DOAs could be conceptualised by the three-factor model(Fig. 1). There is a known familial basis as a predisposing factor. In sleepwalking, the odds of having sleepwalking increased with the number of parents affected, increasing from 3 times to 7 times when both parents had a history of sleepwalking.[7]

Genetic studies have been limited, and some reported the association of DOAs with *HLA-DQB1*05:01*.[8,9] Apart from the genetic effect, any conditions resulting in NREM instability would precipitate or prime DOAs.[10] Factors that deepen sleep, such as compensation sleep after sleep deprivation and the use of certain medications like hypo-sedatives (including benzodiazepines and Z-hypnotics), are possible in inducing DOAs in predisposed individuals, especially with polypharmacy.[11] Conditions that result in sleep fragmentation, such as stress, chronic use of alcohol, and sleep disorders such as sleep apnoea and periodic leg movement, could prime the occurrence of DOAs.[10] These precipitating factors are important in clinical management, as they are potentially modifiable or treatable with a parallel reduction of DOAs occurrence. Moreover, these factors are particularly vital in adult DOAs. Most DOAs occur in childhood, and only a minority would persist into adulthood. For those with adult onset, or having a recurrence of DOAs after long quiescence, it would be vital to look for these precipitating factors.

Table 2: Clinical characteristics and demographics of confusional arousals, sleepwalking and night terror (Developed by author)

	Confusional arousals	Night terror	Sleepwalking
Demographics	Infants, toddlers	Toddlers	Older children
Clinical features:			
Autonomic manifestations such as sweating, tachycardia	Yes	Strong	+/-
Emotion	Yes, crying and agitation	Strong	+/-
Vocalisation	Moaning, crying	Loud screaming	+/-
Movement	Thrashing around bed	+/- simple movement	Simple to complex
Duration	5-15 minutes, may take up to half an hour	A few minutes	Minutes

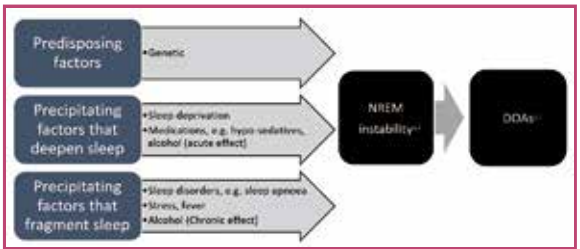

Fig. 1: Three factors model of Disorder of Arousals (DOAs) (Adapted from reference 10- Pressman MR. Factors that predispose, prime and precipitate NREM parasomnias in adults: clinical and forensic implications. Sleep Med Rev 2007; 11: 5–30)

REM SLEEP BEHAVIOUR DISORDER (RBD)

Another major category of parasomnias is REM-related parasomnia, which includes RBD, recurrent isolated sleep paralysis and nightmare disorder. Among them, RBD is chracterised by the dramatic nocturnal behavioural manifestation and resultant sleep-related injuries. RBD is a distinct REM parasomnia characterised by motor activities in response to vivid, often unpleasant and violent dreams, and by a loss of normal skeletal muscle atonia during REM sleep.[1] Patients with RBD may exhibit a wide range of behavioural manifestations during sleep, ranging from simple acts, such as sleep talking and shouting, to vigorous motor activities of dream enactment, such as punching, kicking, and jumping from bed.[1] Sleep-related injuries are, therefore, common sequelae and often the presenting symptoms. Clinical, and epidemiological studies of RBD reported a high prevalence of sleep-related injury at 80%[12,13], and the potentially sleep-related violent behaviours have forensic implications and consequences.[14] Distress and injuries to self and bedpartners are common and may often be the reason for seeking medical consultation.[15]

In contrast to DOAs, RBD is commonly a disease of older adults, particularly males, with a male to female ratio of 4 to 1 in sleep clinics.[12] There could be a long prodromal period of subclinical behavioural manifestations during sleep of infrequent sleeptalking, shouting or limb jerking before a frank onset and a confirmative diagnosis made at around 50 to 60 years old.[12,13] RBD has a prevalence of 1-2% in the general population.[12,13] It has important clinical implications in terms of a high risk of sleep-related violence and high specificity in predicting neurodegeneration.

Idiopathic RBD (iRBD) has been identified as an early precursor of α-synucleinopathy, such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Longitudinal studies have consistently found that over 30% of patients with iRBD eventually developed neurodegeneration at five years of follow-up.[16,17] At 10 years, the risk increased to 82% and further mounted up to 97% at 14 years.[17] The majority of them converted to PD (43%) and DLB (25%). The high specificity and the prolonged prodromal interval before the full emergence of classic neurodegenerative diseases render RBD an unique opportunity for investigating the neurodegeneration progression and planning for neuroprotective trials.

The elaborate behavioural manifestation of RBD is an expression of dysfunctional REM control, resultant from loss of normal skeletal muscle atonia during REM sleep, leading to the dream-enacting behaviours. Based on animal models, lesioning at the sublaterodorsal nucleus (SLD) of the brainstem responsible for REM sleep motor control contributes to RBD pathophysiology.[18] However, the complete pathophysiological model has yet to be unfolded, as one of the core features of violent and unpleasant dreams in RBD has not been well understood. In iRBD patients, α-synuclein in the peripheral autonomic nervous system had been identified in organs such as the colon and skin. Overall, RBD fits in the caudo-rostral topographical sequence of Braak staging model of PD.[19]

ASSESSMENT AND DIFFERENTIALS

Different from other clinical disorders, patients of parasomnia are often poor historians of their sleep

problems as they may be unaware of their nocturnal manifestations. Hence, it is important to include their bedpartners and family in the assessment. With aids from the readily available audio-visual recording on mobile phones, details about the sleep events could be carefully reviewed and examined during interviews. An important differential of sleepwalking is nocturnal frontal lobe epilepsy (NFLE), a seizure presumably of frontal lobe origin. NFLE presents with attacks ranging from brief motor manifestations to hyper-motor seizures and sometimes followed by prolonged complex ambulatory behaviours.[20] In addition, RBD patients may present with complex parasomnia with both RBD and sleepwalking features. The characteristics of sleepwalking, RBD and FLE were compared in Table 3.

Table 3. Characteristics differentiating sleepwalking and RBD from NFLE (Developed by author)

	Sleepwalking	NFLE	RBD
Age	children	Children to adulthood	Older adults/ elderly
Gender	No sex difference	No sex difference	Male predominant
Clinical characteristics			
Sleep stage taking place	NREM-SWS	Any stage	REM sleep
Timing of the events	Usually at first half of the night when SWS predominates	Shortly after sleep and throughout the night	Latter half of the night when REM sleep predominates
Occurrence per night when there is attack	Mostly once	High frequency/ clustering	A few times
Duration	Minutes	Seconds to minutes	Minutes
Manifestations	Simple to complex behaviours	Stereotypic	Dream enacting

Abbreviations:
RBD: REM sleep behaviour disorder
NFLE: Nocturnal frontal lobe epilepsy
NREM: Non-rapid eye movement
SWS: Slow wave sleep
REM: Rapid eye movement

Atypical presentations may also confuse the clinical diagnosis and differentiation of different parasomnias. For example, adult-onset sleepwalking with various complex behaviours, and RBD of the younger age of onset could confound the correct clinical diagnosis. These atypical presentations mostly have associations with mental stress or illnesses[21,22], medications including hypno-sedatives (for sleepwalking)[22,23] and antidepressant usage (for RBD).[23,24] There were also reports on narcolepsy co-morbid with RBD features, especially for young subjects.[13] Hence, it is important to have comprehensive history-taking, including the physical, mental history, concomitant use of medications and symptoms of other sleep disorders.

Screening tools have been adopted in clinical and research settings to aid diagnosis and monitor progress. The Frontal Lobe Epilepsy and Parasomnias (FLEP) scale is one of the tools to differentiate between parasomnia and NFLE.[25] As for RBD, there is a locally designed and validated questionnaire - the RBD questionnaire-Hong Kong (RBDQ-HK).[26,27] Video-polysomnography is an important tool in the assessment of various parasomnias. It is a confirmative diagnostic tool for RBD, with a demonstration of quantitative loss of muscle atonia, and possible recording of vocalisation or movement during the REM sleep period. For DOAs, PSG is not a mandatory diagnostic tool. The opportunities for catching a DOA episode during the sleep study are much lower than that of RBD. However, polysomnography has an important role in providing supportive features to aid clinical diagnoses and look for co-morbid sleep disorders or differentials for the parasomnias, such as sleep apnoea and periodic leg movement.

MANAGEMENT

Home safety is always one of the key treatment modalities for patients with parasomnias, especially for those with complex movements such as sleepwalking and RBD. Sleep-related injury to patients and bedpartners is of high risk. Home safety with scrutinisation of the sleeping environment, including the furniture around beds, installation of window grille with locks and possibly door alarms. It is advisable to provide quiet guidance to get the patients back into bed instead of waking them from sleep during the event. It is particularly undesirable to wake them up forcefully, as it may result in aggression.

Avoidance of precipitating factors is important in managing DOAs and, to some extent, in managing RBD. Stress management, regular sleep-wake pattern to avoid sleep deprivation, early intervention of physical illnesses such as fever are an effective treatment for the vulnerable predisposed DOAs. For those atypical presentations of DOAs and RBD that medication causation is suspected, the decision to stop or switch the medication should be balanced against the risk of stopping treatment. In the scenario of hypnotics, mostly Z-hypnotics induced sleepwalking, stopping or reducing dosage would help to alleviate the occurrence.[28] Switching to other hypnotics or benzodiazepines offers no guarantee in avoiding the sleepwalking as most hypno-sedatives may share a similar sedative effect. Warning on sleep-related complex behaviours is warranted, especially for longterm usage. Non-pharmacological options, including relaxation techniques and cognitive behavioural therapy for insomnia, should be considered for the treatment of insomnia. Antidepressants have been reported to be associated with a higher prevalence of RBD symptoms. However, its aetiological contribution may not be as simply a direct causative effect as that seen in hypnotics-induced sleepwalking. One study reported withdrawal nor stopping antidepressant did not result in the resolution of RBD symptoms nor restoration of the normal REM atonia.[29] Increasing evidence suggested that antidepressants might merely serve to uncover RBD features in predisposed subjects.

For DOAs, the above treatment modalities are usually adopted as the mainstay of treatment, with reassurance to parents of the longitudinal course of decrease in occurrence when the kids grow up.[1] However, pharmacological treatment may have to be considered for those with potentially dangerous or violent behaviours, or those with frequent attacks that resulted in daytime impairment. There is no controlled trials or

evidence-based guidelines on the treatment of DOAs, and there were only isolated case reports on medications such as clonazepam, melatonin and diazepam. Hence, the use of off-label pharmacological treatment option should be thoroughly discussed with parents. Behavioural and psychological interventions such as relaxation, hypnosis and psychological interventions have been suggested, but there is no strong evidence on the efficacy.[30] One of the interventions is scheduled awakening, which is an attempt to wake up the children briefly at 0.5-1 hour ahead of the usual onset of the DOAs on consecutive nights from 5 days to a month. Three earlier case reports stated the substantial resolution of night terror or sleepwalking of 5 children up to 6-month duration.[31-33] Such scheduled awakening seems to be a simple intervention with low risk profile. However, its efficacy and impact on sleep and daytime functioning have not been well studied. Its efficacy may also be highly selective limited to those with frequent and predictable DOAs with the occurrence at certain well defined timing.

For RBD, pharmacological treatment aims for symptomatic control of nocturnal behaviours. More data have been established for clonazepam and melatonin.[34] A local study demonstrated that clonazepam effectively reduced sleep-related injuries and potentially harmful behaviours in two-third of patients, but residual symptoms are common.[35] As most patients are older adults, cautious titration of medication and monitoring of side effects should be exercised.

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Radiology Quiz

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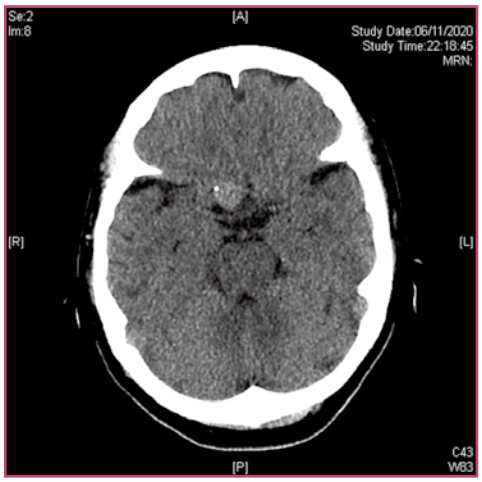

Questions

1. What is the abnormality in this CT brain?
2. What is the differential diagnosis?
3. How would you further investigate?

(See P.28 for answers)

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Parasomnia : an Update on Approach and Management " by Dr Joyce Siu-ping LAM 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 30 April 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. Parasomnia only consists of two sleep disorders - sleepwalking and REM Sleep Behavioural Disorder.
2. Disorders of arousal are regarded as REM sleep-related parasomnia.
3. Confusional arousal most commonly occurs in the infant.
4. Autonomic manifestations are seen in night terror.
5. Sleep deprivation could trigger sleepwalking.
6. REM sleep behaviour disorder is a female predominant illness.
7. Clonazepam is a first-line treatment for night terror.
8. Video-polysomnography is mandatory for a diagnosis of sleepwalking.
9. Hypnotic is associated with an increased risk of sleepwalking.
10. REM sleep behaviour disorder precedes the future development of Parkinson's disease.

ANSWER SHEET FOR APRIL 2021

Please return the completed answer sheet to the Federation Secretariat on or before 30 April 2021 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Parasomnia : an Update on Approach and Management

Dr Joyce Siu-ping LAM

MBChB, MRCPsych, FHKAM(Psych), FHKCPsych
Specialist in Psychiatry

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

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Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to March 2021 Issue

Optimal Management of Pregnant Hepatitis B Carriers to Achieve Complete Eradication of Hepatitis B Infection in Hong Kong

1. T **2.** T **3.** F **4.** T **5.** T **6.** F **7.** T **8.** T **9.** F **10.** T

Management of Childhood Obstructive Sleep Apnoea : An Update on Recent Evidence

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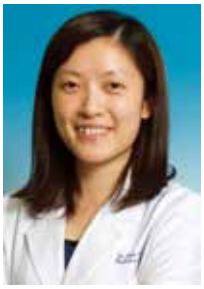

Dr AU Chun-ting Dr Kate CC CHAN

INTRODUCTION

Sleep disordered breathing (SDB) is a spectrum of sleep disorders ranging from simple or primary snoring to obstructive sleep apnoea (OSA), affecting 3-5% of children in Hong Kong. Snoring is the hallmark symptom of OSA. However, the diagnosis and the severity of OSA has to be confirmed with nocturnal polysomnography (PSG), as there is a substantial proportion of children with simple snoring without detectable apnoeas and hypopnoeas during sleep. The first-line treatment of childhood OSA is adenotonsillectomy (AT), i.e. surgical removal of enlarged tonsils and/or adenoid, which is the major cause of OSA in children.

SUBTYPES OF CHILDHOOD OSA

It has been suggested that childhood OSA should be separated into two different subtypes, one characterised by adenotonsillar hypertrophy and normal body weight, and the other characterised by overweight and obesity. Our recent prospective case-control family study showed that the heritability of OSA severity index and familial aggregation of OSA were significant only in overweight individuals but not in normal weight individuals. Genetic variance of obstructive apnoea hypopnoea index (OAHI) among overweight subjects was also significantly greater than normal weight subjects. The difference may be attributed either to a stronger genetic component in the overweight subgroup, or a stronger environmental component in the normal weight subgroup, or both.[1] These findings provide further support to separate childhood OSA into normal weight and overweight subtypes. The pathophysiology of OSA in overweight children is more similar to that of adults, while the normal weight subtype is more likely to be a distinct disease entity unique to children related to adenotonsillar enlargement.

NEW ANATOMIC MARKERS OF CHILDHOOD OSA

Apart from adenotonsillar enlargement and obesity, some anatomic markers have also been recently identified by non-invasive imaging of the upper airway. Sonographic measurement of lateral parapharyngeal wall (LPW) thickness and position of hyoid bone captured by x-ray cephalometry have been found to be associated with higher risks for OSA independent of obesity and tonsil size.[2] Subsequently, it was demonstrated in a family study that LPW thickness was significantly heritable, and it had shared genetic variances with the OSA severity index, suggesting that there are some common genes that contribute to both phenotypes.[3] These findings implicated that these anatomic markers may not only provide extra information about the risk of OSA on top of lymphoid tissue size and obesity, but also help us to understand more about the linkage between childhood and adulthood OSA, potentially paving the way for the future genetic discovery of childhood OSA.

NATURAL HISTORY: FROM CHILDHOOD TO YOUNG ADULTHOOD

Understanding the natural history of a disease helps determine its prognosis and guide its management strategies. Li et al established the Hong Kong Childhood OSA cohort in 2003-2005, which is a community-based cohort consisting of 619 children aged 6-13 years with or without OSA.[4] Over the years, two follow-up studies had been conducted during their adolescence[5] and young adulthood[6] respectively, to reassess their OSA severity objectively by nocturnal polysomnography (PSG). The recent findings from this cohort revealed that among subjects diagnosed to have OSA in their childhood, 30% of them resolved spontaneously in their adulthood. Female sex was the only predictor of resolution of the disease. On the other hand, 22% of those who had no OSA at baseline were found to have incident OSA in their adulthood. Male sex, a higher body mass index (BMI) at childhood, a greater increase in BMI, a higher OSA severity index at baseline, and persistent snoring were independent predictors of incident OSA at follow-up.[6] These findings provide evidence to support risk stratification, disease counselling and prioritisation when we take care of children with OSA.

Another interesting finding from this follow-up study is that the correlation between childhood and adulthood OSA severity index was only significant among subjects with baseline age older than ten years old.[6] This suggests that subjects with OSA diagnosed at their early adolescence tend to persist, while those diagnosed in early childhood were less likely to persist. This suggests that childhood OSA should be further divided into two subtypes according to age, with the disease in adolescence phenotypically more akin to the adult type and thus more likely to persist, while disease in earlier childhood without obesity has a higher chance of spontaneous resolution over time.

IS CHILDHOOD OSA ASSOCIATED WITH LONG TERM ADVERSE OUTCOMES?

Both adulthood and childhood OSA have been recognised to be an independent risk factor for adverse cardiovascular outcomes such as hypertension. However, whether childhood OSA carries any long-term effect on cardiovascular outcomes was largely unknown. A recent study addressed this issue with PSG and 24-hour ambulatory blood pressure monitoring data obtained from a 10-year follow-up study of the previously mentioned Hong Kong Childhood OSA cohort. The study found that subjects with moderate-to-severe OSA during their childhood had higher nocturnal systolic blood pressure (SBP) (adjusted mean 6.5 mm Hg) and reduced nocturnal dipping of SBP (adjusted mean 4.1%) during their young adulthood, regardless of the presence of OSA at follow-up. Those with moderate-to-severe OSA during their childhood had a 2.5-fold increased risk of hypertension and 1.3-fold increased risk of a non-dipping pattern of SBP at follow-up.[7] These findings suggest that there is a threshold effect between childhood OSA and adult BP abnormalities, as only moderate-to-severe OSA was significantly associated with adverse outcomes. Some recent studies have reported that treatment of OSA in children improved their blood pressure[8] and cardiac function.[9] These findings once again highlight the importance of early diagnosis and treatment of OSA in children in order to reduce the cardiovascular risks in their adulthood.

DRUG-INDUCED SLEEP ENDOSCOPY IN CHILDHOOD OSA

Polysomnography (PSG) remains the current gold standard in OSA diagnosis. However, childhood OSA is a heterogeneous disease, and some children may have multiple anatomic or functional causes contributing to the development of the disease. In fact, residual OSA is common after adenotonsillectomy, suggesting that removal of hypertrophied adenotonsillar tissue alone is not universally effective for all children with OSA. Moreover, PSG does not provide information on the site(s) of obstruction. Therefore, direct upper airway evaluation by drug-induced sleep endoscopy (DISE) has been proposed in recent years to evaluate the obstruction level(s) and guide treatment strategies. Sleep nasoendoscopy was first described in the early 1990s and subsequently renamed DISE by Kezirian and Hohenhorst in 2005.[10] DISE involves assessing the upper airway using a flexible endoscope while the patients are in a pharmacologically induced sleep-like state. It has the advantage over awake nasopharyngoscopy to detect dynamic upper airway collapse that may occur exclusively during sleep but may not be appreciated when the patient is awake.

Indications for DISE in children are still evolving. DISE is commonly used to assess for the site(s) of obstruction in children with persistent OSA after adenotonsillectomy to guide subsequent management. It is important to be aware that many children have multilevel obstruction.[10] A systematic review reported that at least one site of obstruction could be identified in children who underwent DISE.[11] In children with persistent OSA after adenotonsillectomy, common sites of obstruction include tongue base, adenoids secondary to regrowth, inferior turbinates, velum and lateral oropharyngeal walls.[10,11] DISE also benefits patients with concern for occult or sleep-state dependent laryngomalacia and prior to hypoglossal nerve stimulator treatment.[10] Although not a routine practice, trachea and bronchi may also be examined during the procedure for children with severe OSA or those with hypotonia to examine for tracheal or bronchial collapse.[12] Additional manoeuvres such as chin lift, jaw thrust, or lateral sleep position can also be incorporated into the procedure to assess airway obstruction effects in response to closed-mouth breathing, mandibular repositioning, and positional therapy.[10]

DISE has also been performed to identify obstruction levels to guide surgical targets or interventions to alleviate the obstruction prior to adenotonsillectomy, particularly in children at high risk for persistent OSA after surgery, i.e. those with obesity, severe OSA, syndromal disease and craniofacial anomalies.[10] However, this practice remains controversial because some believe that airway dynamics change significantly after adenotonsillectomy, contributing to the low yield of pre-operative evaluation with unnecessary costs and operative time.[12] It has been advocated that DISE is generally not indicated for surgically naïve children with classic OSA attributable to adenotonsillar hypertrophy, as the chance that DISE would alter the surgical plan is low.[13] On the other hand, some suggest performing DISE to evaluate OSA children with small tonsils and adenoids. DISE prior to surgery found a positive correlation between the tonsil size and the degree of tonsillar obstruction or lateral pharyngeal wall collapse.[14,15] Therefore, performing DISE as a part of initial surgical evaluation may help to differentiate between obstructive tonsils from non-obstructive ones.

During DISE, medications are given to induce a sleep-like state. One major controversy about DISE procedure concerns whether a drug-induced sleep state is comparable with natural sleep. A study reported that major respiratory parameters of OSA in light sedation do not have significant changes when compared to natural sleep.[16] Propofol is a common anaesthetic agent used in adult DISE. However, studies demonstrated that propofol use is associated with deeper sedation, increased airway collapse and more oxygen desaturations.[17,18] Common medications used in paediatric DISE include dexmedetomidine and ketamine.[10] Dexmedetomidine can replicate non-rapid eye movement (non-REM) and has been preferred for its overall safer profile based upon haemodynamic stability.[13,18,19] Interestingly, dexmedetomidine and ketamine-based DISE has been shown to lead to a significantly higher rate of change in the therapeutic decision.[13] However, no anaesthetic agents are currently able to replicate rapid-eye-movement (REM) sleep, and the use of DISE in children with isolated REM obstructive disease requires cautious interpretation.[10] The utilisation of the Bi-spectral index to objectively measure the sedation depth may help guide the appropriate sedation level for airway assessment during DISE.[13]

DISE offers the potential to evaluate the obstruction site(s) in children with OSA, and to guide management decision-making to improve treatment outcomes. Currently, studies systematically evaluating the impact of DISE-directed OSA management on treatment outcomes are limited.[13] A systematic review reported that DISE changed surgical decisions for 30% of children with OSA and allowed the management plan to address multiple obstruction levels, although whether it provides additional benefit on treatment outcomes remains uncertain.[13] A small paediatric OSA cohort study found individualised, multilevel, DISE-directed operative therapy was associated with substantial improvement in subjective measures of sleep.[20] Other studies demonstrated significant improvement in objective polysomnographic measures with DISE-directed surgery in children with OSA, but most of these studies were uncontrolled.[13] Currently, no recognised DISE phenotype can predict a successful outcome after surgery[11]. One major barrier to moving the DISE research forward is the significant variation in the extent of evaluation and scoring systems used to document obstruction sites.[12] Thus far, six different scoring systems have been developed to report paediatric DISE findings.[10] Therefore, there is an immense need for a validated and universally accepted scoring system to provide a reproducible clinical assessment of the upper airway and to standardise clinical and research communication between clinicians and researchers for future research. Moreover, although DISE is generally regarded as a safe procedure, it still carries potential adverse complications related to the procedure, anaesthesia or sedation. Important adverse events include respiratory depression, desaturations, cough, laryngeal spasm and aspiration[21]. Therefore, the potential benefits and risks should be carefully considered and communicated with the patients and families.

SUMMARY

Childhood OSA is a common condition, and its long-term outcomes and relationship with adulthood OSA have been recently revealed. Early diagnosis and appropriate treatment are essential to avoid long-term adverse clinical outcomes, especially for those with moderate-to-severe disease and overweight/obesity. More research is needed to investigate how this heterogeneous disease can be better characterised so that more precise and appropriate management can be offered to each patient.

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A Brief Perspective on the Diagnosis and Treatment of Obstructive Sleep Apnoea

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BACKGROUND OF SLEEP DIAGNOSTICS

Obstructive sleep apnoea (OSA) is a common disorder and is known to be associated with cardiovascular morbidities.[1] Four types of devices are available for diagnosing OSA. Polysomnography (PSG), also known as type I device, is the gold standard for diagnosis, but its resources are demanding.[2] It provides the most comprehensive assessment from a minimal of 7 physiological parameters, which include electroencephalography (EEG), electrooculography (EOG), chin electromyography (EMG), ECG, airflow, respiratory effort, and oxygen saturation. Type II devices are similar to type I, except that body position and leg movement recordings are optional, and no attendance is required. Type III devices consist of a minimal of 4 parameters (mainly without EEG, EOG and EMG) with a minimum of 2 channels to assess respiration. Type IV devices consist of a minimum of one parameter. Type I devices are used in sleep laboratories or centres where there is real-time monitoring by on-site technicians. Type III devices can be performed without attendance because of the relative simplicity and, thus, can be performed at home. As both the public and healthcare workers have had increased awareness of OSA over the years, home sleep test (HST) using type III devices have evolved as an important alternative diagnostic tool in recent years. Type IV devices are not recommended to be used as a diagnostic tool.

DEVELOPMENT AND ROLE OF TYPE III DEVICES IN DIAGNOSING OSA

In the 1997 practice parameters of the former American Sleep Disorder Association (now the American Academy of Sleep Medicine, AASM), type III devices were not recommended as a diagnostic tool for diagnosing OSA, as there were very limited data supporting the use of type III devices as a diagnostic tool.[2] As more clinical studies on ambulatory devices have shown favourable data, subsequent recommendations of the updated guidelines suggested that type III devices can be considered for diagnosing OSA, as stated in the AASM practice parameters issued in 2003, which was further supplemented by the clinical guidelines published in 2007.[3,4] However, it should be noted that the recommendation is for patients with a high pretest probability of OSA and without significant comorbidities. This implies that patients who are planned to undergo HST should be seen by clinicians for the assessment of possible OSA before the test, as symptoms of excessive daytime sleepiness and snoring are not specific for OSA. Moreover, the limited data collected by type III devices can undermine the accuracy of diagnosis; choosing patients with a high pretest probability of OSA improves the posttest probability of correct diagnosis.

One of the intrinsic weaknesses of type III devices is that they are unable to determine the exact total sleep time (TST). Therefore, the apnoea hypopnoea index (AHI) cannot be determined. Some type III devices use alternative terms such as "respiratory event index" as the equivalent parameter to document the severity of OSA. Although the respiratory indexes can be derived from the recording time, newer devices use actigraphy to estimate the sleeping period more precisely, which is more accurate than the recording time. Nevertheless, most HST tends to underestimate the severity of OSA. Thus, a negative HST in patients with a high pretest probability of OSA warrants a PSG to rule out mild OSA. As there is no EEG recording, sleep staging is not possible. Therefore, if OSA occurs predominantly in REM, it might not be identified; this under-diagnosis potentially applies to other REM-related sleep disorders.

Intuitively, the utilisation of HST can save substantial hospital resources as conducting sleep studies at home cuts down the costs of hospital beds, PSG consumables and technician/nursing manpower. It also potentially saves some opportunistic costs for patients, e.g. taking a day off for hospital admission doing PSG. Inevitably, some HST would be technically inadequate, leading to data loss, as there is no real time technical monitoring during the test as in PSG. Patients might have slept badly, and night-to-night variation can contribute to false negative HST. However, a negative or technically inadequate HST usually require PSG to confirm the presence or absence of sleep disordered breathing, as suggested by the clinical guidelines. Such sequential testing might increase the diagnostic costs. The recent popularity of HST has brought up interest in more in-depth clinical research addressing different aspects of this mode of diagnostic tool. For example, a study addressing technically inadequate HST showed that older patients were more likely to have OSA in technically inadequate or normal HST.[5] This finding implies that in certain subsets of patients with high pretest probabilities of OSA, a poorly performed HST might not be completely useless. Reviewing the raw data of technically inadequate HST, if available, would be more informative than just taking the computer-

generated summary report. Parameters such as the overnight pulse oximetry, numbers of apnoea/hypopnoea episodes may offer interpretative insights rendering the arrival of a reasonable conclusion in relation to the clinical context.

TREATMENT OF OSA: CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)

OSA is associated with resistant hypertension,[6] atrial fibrillation,[7] type II diabetes[8] and cardiovascular accident.[9] Therefore, the treatment of OSA aims not only to reduce the symptoms of snoring and excessive daytime sleepiness but also to reduce the risk of developing other comorbidities. Nasal continuous positive airway pressure (CPAP) is a common treatment for patients with OSA. A CPAP compliance of over 4 hours per night for at least five nights/week is commonly considered acceptable adherence. However, non-adherence to CPAP is frequently encountered and highly variable between 29-83%.[10,11] CPAP compliance is one of the most challenging aspects of managing patients with OSA. Obstacles to CPAP compliance are multidimensional. Some patients feel overwhelmed with the setup of CPAP; some may find the wearing of the CPAP mask very cumbersome to get used to. There can also be technical issues, financial constraint, or physical constraint to accommodate CPAP. Psychological factors such as personality trait with low self-efficacy or lack of motivation could affect how well patients can adapt to a change in lifestyle after using CPAP.[12] Common technical problems such as mask leakage or mouth breathing, leading to excessive pressure delivery and aerophagia, can be problematic, especially in patients using auto-CPAP. Nasal symptoms with CPAP are not uncommon and can be alleviated by using a steroid spray.[13] Addressing problems in using CPAP via early follow up, providing intensive supervision and education in a problem-oriented approach has been shown to improve treatment success and compliance.[10,14] However, this is difficult to implement in the public sector because of the constraints in resources. Telemedicine has been shown to supplement this gap and to improve acceptance and compliance.[15] The role of auto-CPAP in improving compliance is very marginal.[16] For patients who cannot tolerate CPAP, switching to a bi-level device has been advocated as an option. However, the inspiratory pressure or expiratory pressure in the bi-level device might not be significantly lowered, though the tolerance and compliance had been reported to be significantly improved.[17] It is also not clear which group of patients will benefit most from this strategy, especially given that the bi-level device is significantly more expensive than CPAP.

NON-CPAP TREATMENT

Alternative non-CPAP treatment options are important for those who ultimately cannot tolerate CPAP. Oral appliances or dental devices are a popular choice due to their convenience in application and portability. Self-reported compliance rate could be as high as 80%.[18] Common side effects include painful temporal-mandibular joints, increased salivation and drooling. For clinical efficacy, patients need to have healthy native teeth for the optimal fitting of the device; therefore, patients should be referred for a proper dental assessment. Furthermore, dental devices should be custom-made by qualified dentists.[18,19] Compared to CPAP, dental devices achieve less prominent improvement in the AHI, in the minimal oxygen saturation level, and in excessive daytime sleepiness.[18,20] Patients should undergo sleep study while on dental devices in order to assess the efficacy of treatment, and should be referred for device adjustment if necessary.[19]

For positional OSA, i.e. when OSA events are more prominent in the supine position, positional therapy (PT) might be considered if patients cannot tolerate other forms of treatment. The definition of positional OSA is not well defined but is usually taken as when the supine AHI is twice or more than the non-supine AHI. Intuitively, avoiding the position in which the majority of OSA occurs would reduce the AHI. PT can be as simple as a tennis ball or a semi rigid backpack attaching to the back, or as sophisticated as a supine vibration alarm to stimulate the patient to switch from supine to lateral position.[21] In general, the effect of PT in reducing AHI and daytime symptoms seems to be mild though more favourable than inactive control, and compliance has been reported to be better than CPAP.[22] The effect of PT might be more promising in patients with an absolute minimal non-supine OSA, in addition to the conventional supine/non-supine AHI ratio of > 2.[21] As there are no guidelines on the routine use of positional devices, patients should be assessed by clinicians who are experienced in sleep medicine before choosing such devices for the treatment of OSA. More research is needed to define the most suitable patient groups, cost effectiveness and long-term benefits of PT.

Myofunctional therapy (MT) is a treatment for dysfunctions of the muscles of the face and mouth.[23] It has also been used for the treatment of OSA, more often in paediatric patients,[24,25] as children are probably less tolerant of CPAP, dental devices or positional therapy. MT appears to be able to reduce daytime symptoms and improve sleep quality, though the efficacy in other parameters is less certain.[26] There is no consensus on when MT should be considered and for how long. Data on hypoglossal nerve stimulators are promising in selected patient groups,[27,28] and it has been approved in the U.S as a treatment for OSA.[29,30] Bariatric surgery can be considered in obese patients who are motivated to undertake weight loss, as maximal improvement of AHI is associated with ~25% weight loss.[31,32] In some public hospitals, patients with BMI > 30 Kg/m^2 can be referred for consideration of bariatric surgery. Upper airway surgery aims to correct anatomical abnormalities which contribute to airway collapse leading to OSA. The efficacy can be variable as multiple sites of airway collapse can occur, and there are many different types of surgical procedures. There is no established medical treatment for OSA in the literature,[33,34] However, the augmentation of genioglossus activities by atomoxetine and oxybutylin in a recent study has shed light on the possible development of drug therapy targeting at various mechanisms of OSA.[35]

THE WAY FORWARD

As a result of the evolving treatment choices, phenotyping OSA and providing personalised therapies has become a hot topic for the optimal management of patients with OSA. Foreseeably in the future, a combination of OSA therapeutics might be available for treating OSA instead of monotherapy at one time.

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Daytime Sleepiness : An Update on its Assessment and Management

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DAYTIME SLEEPINESS - HYPERSOMNOLENCE

The nosology of disorders with daytime sleepiness was recently updated in Diagnostical and Statistical Manual of Mental Disorders, fifth edition (DSM-5)[1] and the International Classification of Sleep Disorders, 3rd edition (ICSD-3)[2]. In ICSD-3, hypersomnolence is a term describing excessive daytime sleepiness, which is "defined as inability to stay wake and alert during the major waking period in the daytime, resulting in irrepressible need for sleep or unintended lapses into drowsiness or sleep".

DISORDERS CAUSING DAYTIME SLEEPINESS

Disorders causing excessive daytime sleepiness can be divided into those presenting with disrupted nocturnal sleep (see Table 1, for example, insomnia disorder, sleep related breathing disorders [SRBD, including obstructive and central sleep apnoea syndrome], restless leg syndrome, periodic limb movement disorder), circadian rhythm problem, and those with a supposed central cause of origin (central disorder of hypersomnolence). The degree of sleepiness could vary from mild (e.g., falling asleep in boring situations) to severe (falling sleep suddenly, as a sleep attack). Paradoxically, children with sleepiness may present with inattention, hyperactivity, or emotional lability. The sleepiness may be alleviated by naps in some patients, but in others, this is not helped by increased hours of total sleep time at all. There is no minimum duration of nocturnal sleep required for diagnosis in ICSD-3, but in DSM 5, it requires a main sleep period of 7 hours at least. The duration of hypersomnolence would be at least 3 months in most of the disorders under the diagnostic category with central causes (except hypersomnia due to a medication or substance).

ASSESSMENT

A comprehensive history with basic sleep pattern and symptomatology of both daytime sleepiness and nighttime sleep is mandatory for a good differential diagnosis. Often, the use of sleep log and sleep diary can aid in the accurate reporting and evaluation of daytime and nocturnal sleep pattern, whereas more objective evaluation can be achieved by actigraphy. Subjective evaluation of severity of sleepiness can be made by the Stanford Sleepiness Scale (SSS)[3] or the more commonly locally validated instrument - Epworth Sleepiness Scale (ESS)[4]. ESS is an eight-item questionnaire for measuring the propensity of dozing off/falling asleep in different circumstances, with its scores range from 0 to 24. For screening of narcolepsy, the Hong Kong Chinese version of Ullanlinna Narcolepsy Scale (cUNS) was validated in 2000.[5] The objective measurement of daytime sleepiness is assessed by Multiple Sleep Latency Test (MSLT)[6,7,8] (measuring one's propensity to fall asleep and subjects with mean sleep latency less than 8 minutes are considered to have daytime sleepiness) or Maintenance of Wakefulness Test (MWT) (measuring one's ability to remain awake during the test).[8,9,10] Nocturnal polysomnography (n-PSG) would be needed before MSLT/MWT and is vital in diagnosing sleep related breathing disorders, periodic limb movement disorder and parasomnia.

Table 1: Differential Diagnoses for Daytime Sleepiness (Adapted and Modified from ISCD-3[2])

Common causes of daytime sleepiness	
Insufficient Sleep Syndrome	
Sleep Related Breathing Disorder	Obstructive Sleep Apnoea Syndrome
Insomnia Disorder	(daytime sleepiness as a comorbid symptom)
Circadian Rhythm Sleep Wake Disorders	
Restless Leg Syndrome	
Periodic Limb Movement Disorders	
Hypersomnia	Due to a Medical Disorder Due to a Medication of Substance Associated with a Psychiatric Disorder
Rare central disorders of hypersomnolence	
Narcolepsy	Type 1
	Type 2
Idiopathic Hypersomnia	
Kleine-Levin Syndrome	

COMMON CAUSES OF DAYTIME SLEEPINESS (EDS)

Insufficient Sleep Syndrome

Sleep deprivation is the commonest cause of excessive daytime sleepiness. It is a global issue and is common in the local population across all age groups in Hong Kong.[11] The sleep time of patients is shorter than that expected of their age with usually a compensatory sleep during weekends or holidays. Sleep logs, and if available,actigraphy, preferably for at least 2 weeks would be helpful in making an accurate diagnosis. Extending the sleep duration would often help to

normalise their sleepiness.[12] Sleep hygiene and education would be needed in management, but this alone may not be adequate, as shown by the lack of a significant impact on the sleep duration or pattern amongst the adolescents by a school-based sleep education programme in a local study.[13]

EDS Related to SRBD

Obstructive sleep apnoea (OSA) is a common disorder with a local prevalence of 4.1%.[14] Besides daytime sleepiness, snoring, dry mouth, observed cessation in breathing, subjective choking feeling, drooling of saliva, morning headache, nocturnal enuresis and sexual dysfunction are all symptoms of OSA. Continuous positive airway pressure (CPAP), dental appliance and surgery are all common treatment modalities for OSA.

Hypersomnia due to a Medical Disorder / Mental Disorder / Medication or Substance

Multiple medical conditions can present with hypersomnolence, including neurodegenerative diseases (e.g. Parkinson disease), brain trauma, stroke or tumour (lesions in posterior and lateral hypothalamus or midbrain), infection, hypothyroidism, metabolic encephalopathy, genetic disorder (e.g. myotonic dystrophy, Niemann Pick type C, Prader-Willi syndrome) and other systemic inflammatory conditions. For those sleepiness associated with mental disorder (for instance, depression, bipolar disorder, and seasonal affective disorder), the result of MSLT is usually normal but the patients may stay in bed for long duration. Hypersomnia due to a medication or substance is the only category which does not require a minimal duration of 3 months of EDS symptoms, and a causal relationship between medication or substance use or withdrawal and the subsequent daytime sleepiness, is needed to establish this diagnosis. Treatment includes the management of the underlying causes but adjunct stimulant treatment may be helpful in some cases.

NARCOLEPSY TYPE 1 VS TYPE 2

Narcolepsy is a much rare disorder in comparison to obstructive sleep apnoea[14] and insufficient sleep syndrome (more than 40% children of age 6-11 in Hong Kong slept less than 9 hours in 2012).[15] The highest prevalence of narcolepsy was reported amongst Japanese of 0.18% and the lowest in Jews of 0.002%[16], with a local prevalence of 0.038%[17]. Common age of onset is from early teens to twenties. Apart from Besides long-term burden directly linked to excessive daytimes sleepiness, narcolepsy is also reported to have an increased risk of medical and psychiatric comorbidities.

Patients with narcolepsy type 1 present with at least 3 months of hypersomnolence, with either 1) cataplexy (sudden symmetrical muscle weakness without loss of consciousness, usually precipitated by positive emotions [usually by laughter but rarely by other sensory stimulus][18]), plus a MSLT result of ≤ 8 min with ≥ two SOREMPs (one of these 2 SOREMPs can be replaced by a nocturnal SOREMP in the preceding n-PSG; normally one will not expect to see onset of REM sleep until 60-90 minutes after falling asleep), or 2) a low CSF hypocretin-1 concentration ≤ 110 pg/mL or less than one-third of the mean values in the population. Type 2 differs from type 1, at which there is no cataplexy with a relatively normal CSF hypocretin level. Although cataplexy may also occur in Niemann-Pick type C, Prader Willi Syndrome, or multiple sclerosis, presence of cataplexy is usually regarded as pathognomonic of narcolepsy. Thus a detail history will usually be able to differentiate from mimicry cataplexy-like symptom including syncope, epilepsy, drop attacks and hyperekplexia.[19] Recently, an altered sleep stage transition directly from awakening/non-REM stage 1 sleep to REM sleep (skipping NREM stage 2 and 3 sleep) in either n-PSG or MSLT was found to be more common in type 1 narcolepsy than other sleepiness disorders.[20]

The classical tetrad syndrome of narcolepsy, in addition to sleepiness and cataplexy, includes also sleep paralysis and sleep related hallucinations. Disturbed nocturnal sleep is considered as the fifth core symptom in narcolepsy.[21] An increased risk of developing REM sleep behaviour is also noticed in the narcolepsy patients.[22,23]

It is worth noting that a MSLT result of ≤ 8 min[24] with concomitant ≥ two SOREMPs[25] is also a common finding in patients with severe SRBD. Therefore, other causes of hypersomnolence (for example, SRBD and circadian rhythm problem) are to be treated before making a definitive diagnosis of narcolepsy, albeit SRBD is also commonly comorbid with narcolepsy.

Based on the earlier findings of HLA-DQB1*0602 (almost 100% in type 1, vs 45% in type 2 vs 12-38% in the control population) 2, loss of hypocretin/orexin neurons in the hypothalamus (more severe in type 1)[26], elevated levels of anti-streptolysin O titres[27] and antibodies against Tribble homolog 2 after narcolepsy onset[28], an autoimmune destruction of hypocretin neurons is proposed as the pathology underlying narcolepsy type 1. This postulation is further echoed by the surge of narcolepsy after the 2009 H1N1 pandemic in China[29] and after the Pandemrix vaccination in some countries[30]. More evidence for autoimmune origin of narcolepsy type 1 is reported by the findings of autoreactive CD4+ T cells and hypocretin-specific CD8+ T cells[31] and of increase circulating B cells and CD4+ follicular T cells in narcolepsy type 1 patients[32]. On the other hand, it remains unclear whether narcolepsy type 2 is a milder form of type 1 or a disorder with a separate pathology.

The practice guideline by American Academy of Sleep Medicine (AASM) for pharmacological and behavioural treatment for narcolepsy was published in 2007[33]. Stimulant treatment such as methylphenidate, modafinil and armodafinil are effective in treating daytime sleepiness whereas serotonergic antidepressants are effective for cataplexy. Sodium oxybate is effective for both daytime sleepiness and cataplexy, and it may also be used for sleep paralysis and sleep related hallucinations with improvement in nocturnal sleep. Scheduled nap is helpful to counteract the sleepiness, but it is not adequate as primary treatment.

There are ongoing new medications and other

modalities of therapy. Pitolisant, a selective histamine-3 receptor antagonist/inverse agonist, which enhances histaminergic activity, was approved by FDA for the treatment of daytime sleepiness and cataplexy.[34] Solriamfetol, a dopamine and norepinephrine reuptake inhibitor, was approved by FDA in 2019 for treatment of daytime sleepiness[35]. An updated review of other treatment modalities under development includes immunomodulation (intravenous immunoglobulin, steroids, plasmapheresis, azathioprine, alemtuzumab and rituximab), non-peptide hypocretin/orexin (ORX)-B agonist, ORX-A replacement, ORX cell transplantation, ORX gene therapy.[36]

IDIOPATHIC HYPERSOMNIA (IH)

Up to two-third of IH patients have been reported to have sleep inertia or sleep drunkenness, presenting as falling asleep repetitively with irritability, automatic behaviour and confusion. In contrast to narcolepsy patients, naps are not refreshing in majority of IH patients. CSF hypocretin/orexin level is preserved in IH patients.[37] The diagnostic criteria of IH include fewer than 2 SOREMPs in MSLT, with either a mean sleep latency ≤ 8 min or with a total 24-hour sleep time ≥ 660 min. The aetiology of IH remained unclear. A recent article with 468 IH patients reported that 64.1% of patients remained to have symptoms of daytime sleepiness despite stimulant treatment[38].

KLEINE-LEVIN SYNDROME (KLS)

KLS is a rare syndrome presenting recurrent episodes of bouts of sleepiness, for at least 2 recurrent episodes of daytime sleepiness lasting from two days to five weeks. Patients are normal between the episodes but during the attack, patient will present at least one of the following features: 1) cognitive dysfunction (anterograde amnesia, depression), 2) altered perception (e.g. derealisation, hallucinations, delusions), 3) anorexia or hyperphagia, 4) disinhibited behaviour (e.g. hypersexuality). Patients can sleep up to 16-20 hours per day and only get up to eat or void without any incontinence during the long sleeping hours. Even when they are awake, they appear exhausted, apathetic and slow in response. The onset usually is in the second decade and is more in male. The clinical course is usually less severe and less frequent with time. Reported treatment modality for KLS includes lithium as prophylactic agent, stimulant treatment for alleviating sleepiness and antipsychotic for psychotic symptoms.[39] A variant of menstrual-related KLS is recurrent sleepiness attacks occurring before or during menses. Its responses to contraceptive pills suggest an underlying endocrine disturbance as the pathology.

CONCLUSION ON APPROACH TO DAYTIME SLEEPINESS

Daytime sleepiness is a common symptom of general population across all ages in Hong Kong. However, it is important for clinicians to be aware of the common causes (for example, abnormal sleep pattern or duration, symptoms of sleep apnoea, other medical or psychiatric causes) and the characteristic features of the rare disorders such as cataplexy symptom, which is pathognomonic of type 1 Narcolepsy. The use of a sleep log and diary, and questionnaires (for example. ESS and cUNS) would be helpful in differentiating the above differential diagnoses in the primary care setting. Appropriate referral to specialists and sleep clinics would be needed for further detail nocturnal PSG and daytime MSLT.

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Clinical Management of Insomnia in Youth: Challenges and Current Evidence

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INTRODUCTION

Insomnia is the most prevalent sleep problem affecting 4%-36% of youths[1-3] and is highly comorbid with medical and psychiatric illnesses. Insomnia may lead to significant negative consequences in youth's lives, including adverse mental and physical health, cognitive impairments, behavioural problems and poor academic performance.[2-4] However, this common distressing sleep problem is often under-recognised and under-treated in clinical practice. The help-seeking behaviour for insomnia is very uncommon, as only 10% of the young people in the community have sought treatment for their sleep problem.[5] Insomnia, when left untreated, is highly persistent (45.8% over one-year interval).[6] In addition, adult patients who had childhood onset insomnia represent a difficult group that might require specific treatment needs compared to the those with adult-onset insomnia.[7] Thus, it is necessary to provide timely and effective insomnia treatment in order to generate substantial health gains and reduce its associated healthcare burden over the long run.

DEVELOPMENTAL CHANGES IN SLEEP

Individual's sleep pattern changes across developmental stages, with a gradual decrease in total sleep time and alterations in sleep structure.[8] During adolescence, there is a marked decrease in slow wave sleep, which is hypothesised as an index of adolescent brain reorganisation.[9] Moreover, a natural delay in the circadian rhythm represents another distinctive sleep feature during adolescence,[10] which explains the high prevalence of preference for eveningness in the youth population. These intrinsic changes in sleep characteristics, together with external factors, such as heavy school burden, excessive media use, and early school start time,[11] may increase the risk of developing sleep problems. For example, local data has demonstrated that the prevalence of insomnia increased from 3.9% to 10.9% across the stages of pubertal development, with the emergence of female predominance in late-puberty.[1] This observation further emphasises the need to timely address this particular sleep problem in the youth population.

OVERVIEW OF INSOMNIA TREATMENT IN YOUTH

Treatment options for insomnia include pharmacological and non-pharmacological approaches, which could be used alone or as a combined treatment. Cognitive behavioural therapy for insomnia (CBT-I) has been recommended as the first-line treatment option for insomnia in the adult population.[12] Currently, there is no clear clinical guideline in managing youth insomnia, but emerging evidence has provided strong support for the clinical efficacy of CBT-I in youth with insomnia.[13] However, the implementation of CBT-I in the youth population is very limited, with pharmacotherapy still being the more common treatment approach in clinical setting, possibly due to the quicker therapeutic effects of medications.

Cognitive Behavioural Therapy for Insomnia in Youth

CBT-I is a multi-component non-pharmacological intervention that targets behavioural, cognitive, and physiological perpetuating factors of insomnia. It consists of strategies aiming to modify and alter maladaptive behaviours and misconceptions towards sleep and insomnia. A typical CBT-I course, as led by trained therapists, lasts for four to eight weeks and covers the following treatment components: stimulus control, sleep restriction, relaxation technique, cognitive therapy, sleep hygiene education and relapse prevention. There is a strong evidence base for the short-term and long-term efficacy of CBT-I for both primary and comorbid insomnia with medium to large effect sizes.[13-15] Nevertheless, CBT-I is not always available in clinical practice mainly as a result of geographical limitations, a perceived high cost to deliver the treatment, and a lack of professionally trained sleep therapists.[16-18] In light of these limitations, alternative modes for delivery of CBT-I (e.g. via digital platforms) have been developed to increase its accessibility and availability of the treatment; these alternative delivery modes have been shown to carry comparable efficacy to that of the traditional face-to-face CBT-I. For example, both objectively and subjectively measured sleep onset latency and sleep efficiency were significantly improved after the CBT-I intervention regardless of the treatment modality (group-based or digitally delivered).[13]

It is notable that CBT-I was found to improve subjective total sleep time in adolescents, but such an effect was not often seen in adults.[13] In addition, the improvement of sleep in response to CBT-I is associated with parallel positive changes in daytime functioning and mood symptoms.[19] Given the high comorbidity between insomnia and psychiatric disorders, as well as the potential impact of insomnia in the trajectory of mood problems, a transdiagnostic approach by targeting insomnia in the context of psychopathology has been suggested.[20] In this regard, there has been some evidence showing that augmenting conventional depression treatment in youth by addressing sleep problem could improve not only sleep but also depression outcome.[21]

Pharmacotherapy for Insomnia in Youth

Currently, there is no sleep medication approved by the US Food and Drug Administration (FDA) in treating insomnia in the youth population. Nonetheless, over 95% of the paediatricians reported having prescribed medications for insomnia in an off-label fashion.[22] Medications commonly prescribed include benzodiazepines, α-receptor agonists, melatonin, sedative medications such as antihistamines and antidepressants.[23-25] Pediatricians tend to manage youth insomnia by adopting a similar approach for managing adult insomnia, because there have been very limited randomised controlled trials (RCTs) to examine the clinical efficacy of hypnotic/sedative drugs in treating insomnia in youth. Several professional bodies, including the American Academy of Sleep Medicine (AASM) and the American Academy of Pediatrics (AAP), have issued consensus statements articulating the necessity of clear guidelines on the safety, tolerance and prescription for medications in this age group.[25,26] It has also been suggested that paediatricians should use sleep medications as an adjunct or prescribe only when behavioural management of insomnia is ineffective in young people.[25,27-32]

Despite the limited evidence on pharmacotherapy for treating insomnia in youths, some drugs, such as melatonin, are available as over-the-counter (OTC) medication and can be easily accessible by the general population. In a national survey, approximately 90% of child psychiatrists in the United States recommended OTC medication for managing insomnia in children and adolescents, with melatonin being the most frequently dispensed drug.[22, 33, 34] A meta-analytic review on the efficacy of melatonin in both child and adult populations reported that melatonin is able to reduce sleep onset latency with a possible dose-response effect.[35] Children with special needs, including those with autism spectrum disorder, attention-deficit/hyperactivity disorder and intellectual disability, are often prescribed melatonin for managing their insomnia.[36] However, RCTs on melatonin specifically conducted in youth are largely lacking. For example, few RCT studies suggested that youth with sleep onset insomnia and delayed sleep phase syndrome (DSPS) might benefit from the administration of melatonin.[36] Nonetheless, the improvement of sleep was not consistently reported in the published trials.[37,38] Moreover, there were only small improvements observed in terms of the functional outcomes, such as daytime functioning and cognitive abilities, following melatonin treatment, and the therapeutic effects on sleep could not be sustained when drug treatment was terminated, which suggested the need for long-term prescription in order to maintain the positive outcome.[39] Although a recently published study provided strong evidence supporting the long-term use (up to 104 weeks) of paediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder,[40] there are very limited data in youths. More studies are needed to explore the long-term safety and efficacy of melatonin use in the youth population.

CHALLENGES IN TREATING INSOMNIA IN YOUTH

In treating youth insomnia, cognitive behavioural strategies should be recommended before the initiation of drug treatment.[24,25,27] However, cognitive behavioural therapy may require additional training and longer doctor-patient time, and the beneficial effect could only be seen after weeks or months. Thus, pharmacotherapy is still the common initial treatment for youth insomnia. Nonetheless, paediatricians reported a wide variation in clinical practice with regard to the dosage and duration of prescription, resulting in potential overdosing or underdosing, and at times involving inappropriate selection of medications.[27,28,41] It is noteworthy to point out that the majority of the evidence and survey data have been derived from western countries whilst there have been very limited studies conducted in Hong Kong. Therefore, local clinical practice regarding insomnia treatment in youth remains largely unknown. Further investigation is needed to understand the practice in the local context.

CLINICAL RECOMMENDATIONS

In general, treatment strategies for youth insomnia should be formulated based on a comprehensive clinical evaluation.[41] Given the close association between insomnia and medical and psychiatric conditions, there is a need to assess the comorbidity and consider adopting a transdiagnostic approach by targeting insomnia during the intervention. As discussed before, the non-pharmacological approach - cognitive behavioural therapy for insomnia - should be the main treatment approach for managing youth insomnia given its emerging, strong clinical evidence. Whilst pharmacotherapy is rarely considered as the initial or sole treatment, it should be used as supplementary to cognitive behavioural therapy or used when cognitive behavioural therapy appears ineffective.[41] When medication is administered, the prescription should be carefully selected based on the clinician's best judgement in accordance with the patient's presenting complaints, disease severity, and comorbidities.[36] Dosage and duration of the medications should be initiated at the lowest level, and gradually increased as necessary under careful monitoring.[41] Moreover, potential pharmacodynamic and pharmacokinetic drug-to-drug interactions with concurrent medications should be carefully evaluated.[36,41] Involvement of parents or caregivers in managing insomnia in adolescents,

especially those younger ones, may also be necessary in order to facilitate the delivery of the intervention and maximise the treatment gains.

CONCLUSION

In summary, insomnia is a common problem in youth, which may result in a constellation of adverse impacts on both physical and mental health. Along with the emerging evidence on the efficacy of cognitive behavioural therapy for insomnia in the management of youth insomnia, non-pharmacological approaches should be considered as the first-line treatment option and be only supplemented with medication when necessary.

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Development of Sleep Medicine in Hong Kong

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INTRODUCTION

Sleep medicine is a relatively young field of medicine, with most discoveries made in the twentieth century. For example, Rapid Eye Movement (REM) sleep[1] was discovered in 1951 and sleep apnoea[2] was described in 1965. With improved understanding of sleep apnoea syndromes[3] in the 1970s and the introduction of Continuous Positive Airway Pressure (CPAP)[4] in 1981, interest in sleep apnoea and demand for treatment heightened in Hong Kong in the 1990s.

EARLY REPORTS OF OBSTRUCTIVE SLEEP APNOEA SYNDROME (OSAS) IN HONG KONG

A case series of 13 overweight OSAS middle-aged adults was reported by the University of Hong Kong (HKU) researchers in 1989.[5] Most of these patients had evidence of hypoxaemia upon daytime blood gas sampling. Three had hypercapnia, while four already had cor pulmonale. Comorbid illnesses were also present in most of the patients. CPAP was offered to 10 patients. A more diverse group of five patients was reported by the Chinese University of Hong Kong (CUHK) team at around the same time.[6] A female patient with severe micrognathia presented with sleep attacks while standing and had already developed polycythemia and pulmonary hypertension. Her sleep-disordered breathing normalised with a permanent tracheostomy. Good response was attained in a paediatric patient in this series with tonsillectomy. CPAP was prescribed to two patients, including one who did not improve after uvulopalatopharyngoplasty (UPPP). Since the early 1990s, Otolaryngologists had used drug-induced sleep video nasoendoscopy to enhance the understanding of OSAS patients' upper airway dynamics.[7]

SLEEP LABORATORIES IN HONG KONG

The gold standard for OSA diagnosis is overnight attended polysomnography (PSG) that monitors sleep stages (as reflected by electroencephalogram (EEG), electrooculogram and chin electromyogram, EMG) and respiratory parameters. From the beginning, it called for the collaboration of Psychiatrists who were running sleep laboratories and Respiratory Physicians who were managing advanced OSAS patients with complications, including respiratory failure. Since the PSG montage was traditionally more focused on sleep staging and limb movements and studied by psychiatrists and neurologists, electrocardiogram, pulse oximetry and channels measuring airflow, thoracic and abdominal efforts were added for OSA diagnosis.

The advent of non-invasive ventilation (NIV) such as CPAP and later, bilevel positive airway pressure (BPAP) also led to a surge in demand for Respiratory Physicians' input. Another OSA treatment that emerged at around the same time as CPAP was UPPP. In combination with tonsillectomy, UPPP is effective in relieving upper airway soft tissue overcrowding in patients with enlarged tonsils, particularly the paediatric population. Otolaryngologists were also being consulted for snoring that disturbed sleeping partners. Hence, the evolving management of sleep apnoea often required collaboration from multiple specialities.

Apart from pioneer sleep laboratories in the 1980s at university hospitals such as Prince of Wales Hospital and Queen Mary Hospital, Haven of Hope Hospital started her sleep and NIV service in 1993. Kwong Wah Hospital Paediatric Department set up a sleep service in 1995. In 1996, three hospitals (Wong Tai Sin Hospital, Kowloon Hospital and Tuen Mun Hospital, TMH) commenced their sleep services. This was followed by sleep services at Pamela Youde Nethersole Eastern Hospital (PYNEH) in 1997 and Ruttonjee Hospital in 1998. With the availability of computerised PSG systems and CPAP suppliers as well as continuing patient needs, sleep medicine became an indispensable service in many Hospital Authority (HA) hospitals. Sleep services were commenced at North District Hospital, Alice Ho Miu Ling Nethersole Hospital, Queen Elizabeth Hospital (QEH), United Christian Hospital (UCH), Caritas Medical Centre and Princess Margaret Hospital too.

SLEEP SERVICE CHALLENGES

Attended overnight PSG is labour-intensive. Registered PSG technologists (RPSGT) hook patients up for PSG and perform real-time CPAP/BPAP titration on treatment nights. They also preliminarily score PSG reports before further analysis by doctors. The first RPSGT was recruited and trained by CUHK/PWH and sent for overseas training in 1986. By 2015, there were 76 RPSGT in Hong Kong. TMH was the first HA hospital to create two full-time sleep laboratory technician posts in 1997 and 1998, followed by QEH and UCH. Most hospitals, however, rely on nurses with or without RPSGT qualification to conduct PSG and support patients on long-term CPAP. Not all sleep

laboratories could afford to conduct PSG attended all-night by staff. Without designated staff, it was difficult to perform manual NIV titration for indicated patients or manual scoring of PSG tracings. Sleep centres were running the risks of missing abnormal findings and providing suboptimal treatment.

The situation of supply not meeting demand was further complicated by commercial CPAP suppliers' attempts to fill the gap. Self-financed home unattended PSG and auto-adjusting CPAP trials without prior diagnosis became available. Since there is no statutory body monitoring of the quality of sleep testing or reporting in Hong Kong, OSA could be over- or mis-diagnosed. Furthermore, if OSAS patients' first CPAP experience were unpleasant, this could impact upon his/her subsequent CPAP acceptance and long-term treatment compliance.

The year 2020 saw the implementation of a 24-hour sleep laboratory service model for adult sleep apnoea at two HA hospitals (PYNEH and TMH). The roles of RPSGT, nurses and doctors in conducting PSG, home sleep assessment tests (HSAT), supporting patients' home CPAP treatment, analysing reports and clinic consultations were recognised, respectively.

HONG KONG SOCIETY OF SLEEP MEDICINE (HKSSM)

Founded in 1993 by Prof Chen Char-nie (CUHK) and Prof Mary Ip (HKU), HKSSM continues to be served by a diverse council of specialists, ranging from Paediatricians, Respiratory Physicians, Otolaryngologists to Psychiatrists. Apart from raising public awareness of sleep disorders, HKSSM supports a RPSGT group and organises regular clinical and scientific meetings, workshops and certificate courses for members. HKSSM is also a founding member of the newly established Asian Society of Sleep Medicine. Since 2013, two International Sleep Medicine Examinations have been organised for doctors. We now have 22 doctors who have received the International Sleep Specialist Designation awarded by the World Sleep Society after passing the examinations. Thirteen applicants have shown interest as we prepare to organise a third examination.

PREVALENCE OF SLEEP DISORDERS AND IMPACT OF SLEEP RESEARCH IN HONG KONG

In a retrospective study of 342 patients presented to the CUHK sleep laboratory between 1986 and 1992, five patients were diagnosed with narcolepsy.[8] This first laboratory-diagnosed Chinese narcolepsy study confirmed a high association with HLA DR2 like the Western population.[9] It also gave a laboratory prevalence of 1.5% and a population prevalence rate in the range of four in 10,000 to one in 100,000. The CUHK group went on to conduct a general population study interviewing 9,851 subjects.[10] Based on clinical-polysomnographic-HLA confirmation, the prevalence rate of narcolepsy in Hong Kong Chinese was found to be 0.034%. All were HLA DRB1-1501 positive, and 50% were DQB1-0602 positive.

Between 1997 and 2000, HKU conducted two important community studies that determined the prevalence of OSAS among middle aged adults in Hong Kong. Based on PSG, it was estimated that 9% of middle-aged men had OSA, and 4.1% were symptomatic with daytime sleepiness.[11] Prevalence of OSAS was lower among middle-aged women at 2.1%.[12] With age, however, there was a 12-fold rise among women from the fourth to the sixth decade. Subsequent HKU OSA research focused on cardiometabolic complications[13-15] and underlying pathogenetic mechanisms. CUHK conducted a community study involving 6447 primary school children, with 619 undergoing overnight PSG.[16] Based on International Criteria of Sleep Disorders version II, the OSAS prevalence for boys and girls was 5.8% and 3.8%, respectively.

As a referral centre for REM sleep behaviour disorder (RBD) patients, CUHK Psychiatry Department has been collaborating with Neurologists to study RBD patients, from links with neurodegenerative diseases[17] to risks of mortality.[18] Based on 205 patients with video-PSG confirmed RBD, it was found that RBD patients had higher mortality if neurodegenerative diseases developed.

To meet the ever-increasing demand for early diagnosis and treatment of OSAS patients, a randomised controlled trial (RCT) was conducted by CUHK Medical Department to compare an ambulatory approach (HSAT and home autoCPAP titration) with hospital-based approach. Home-based approach was found to be non-inferior to hospital-based approach in terms of CPAP usage and clinical outcomes. Patients with suspected OSAS benefited from a shorter waiting time while hospitals saved costs through reserving inpatient beds for acutely ill patients rather than ambulatory OSAS patients.[19]

Apart from research in sleep disorders, CUHK Psychiatry Department conducted the first large-scale cluster RCT in school-based sleep education in Asian countries. The aim was to promote good sleep hygiene practice among adolescents. Unfortunately, while sleep knowledge was enhanced, sleep duration did not improve significantly.[20]

CONCLUSION

More than three decades after the introduction of sleep medicine into Hong Kong, there is finally hope that sleep medicine is being recognised as an essential service in healthcare. OSAS and CPAP treatment are now commonplace. However, through the dedication of researchers and sleep practitioners (from Paediatrics to Medicine, Psychiatry, Otolaryngology, Dental and Maxillofacial surgery) and patients' feedback, we know that treating OSAS does not stop with providing CPAP. As we grow in our understanding of sleep disorders, our efforts to remind all the importance of good sleep for health maintenance and disease prevention should continue unabated.

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				1	2	3
4	5	6	* Certificate Course on Wilderness Medicine 2021 (Video lectures) 7	8	9	10
11	12	* Live Lecture HKMA - HKS&H CME Programme 2021 Topic: 10 Things that you need know about Prostate Cancer (Online) * Certificate Course on Lower Urinary Tract Symptoms 2021 (Video Lectures) 13	* The Hong Kong Neurosurgical Society Monthly Academic Meeting –TBC * Certificate Course on Wilderness Medicine 2021 (Video lectures) 14	* Live Lecture Combating Cardiometabolic Disorders with SGLT2 inhibitors: From Science to Clinical Practice 15	* Live Lecture Advanced in Neurorehabilitation 16	17
18	19	* Live Lecture HKMA-GHK CME Programme Topic: Update on management of Peritoneal Malignancy * Certificate Course on Lower Urinary Tract Symptoms 2021 (Video Lectures) 20	* Certificate Course on Wilderness Medicine 2021 (Video lectures) 21	* Live Lecture Diabetes Remission – Review of Medical Evidence * HKFMS Foundation Meeting * FMSHK Executive Committee Meeting 22	23	24
25	26	* Certificate Course on Lower Urinary Tract Symptoms 2021 (Video Lectures) 27	* Certificate Course on Wilderness Medicine 2021 (Video lectures) 28	* Live Lecture Update in Management of Lung Cancer 29	30	

Date / Time	Function	Enquiry / Remarks
7 WED 7:00 PM	**Certificate Course on Wilderness Medicine 2021 (Video lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Peter Pay-yun CHEE	Ms Vienna LAM Tel: 2527 8898
13 TUE 2:00 PM	**Live Lecture** **HKMA - HKS&H CME Programme 2021** **Topic: 10 Things that you need know about Prostate Cancer (Online)** Organiser: Hong Kong Medical Association Hong Kong Sanatorium & Hospital; Speaker: Dr Darren Ming-chun POON	HKMA CME Dept. Tel: 3108 2507 1 CME Point
7:00 PM	**Certificate Course on Lower Urinary Tract Symptoms 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Bryan Kwun-chung CHENG	Ms Vienna LAM Tel: 2527 8898
14 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed** Organizer: Hong Kong Neurosurgical Society Speaker(s): Dr CHEUNG Wing-lok Chairman: Dr PO Yin-chung Venue: Conference Room, F2, Department of Neurosurgery, Queen Elizabeth Hospital; or via Zoom meeting	Dr Calvin MAK Tel: 2595 6456 Fax. No.: 2965 4061 1.5 points College of Surgeons of Hong Kong
7:00 PM	**Certificate Course on Wilderness Medicine 2021 (Video lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr HO Man-kam	Ms Vienna LAM Tel: 2527 8898
15 THU 2:00 PM	**Live Lecture** **Combating Cardiometabolic Disorders with SGLT2 inhibitors: From Science to Clinical Practice** Organiser: HKMA-KLN East Community Network; Speaker: Dr LI Siu-lung;	Miss Antonia Lee Tel: 3108 2514 1 CME Point
16 FRI 2:00 PM	**Live Lecture** **Advanced in Neurorehabilitation** Organiser: HKMA-KLN City Community Network; Speaker: Prof Lawrence Ka-sing WONG	Ms. Candice Tong Tel: 3108 2513 1 CME Point
20 TUE 2:00 PM	**Live Lecture** **HKMA-GHK CME Programme** **Topic: Update on management of Peritoneal Malignancy** Organiser: Hong Kong Medical Association Gleneagles Hong Kong Hospital; Speaker: Dr Jeremy YIP	HKMA CME Department Tel: 2527 8452 1 CME Point
7:00 PM	**Certificate Course on Lower Urinary Tract Symptoms 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr Berry Tat-chow FUNG	Ms Vienna LAM Tel: 2527 8898
21 WED 7:00 PM	**Certificate Course on Wilderness Medicine 2021 (Video lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr NG Wah-shan	Ms Vienna LAM Tel: 2527 8898
22 THU 2:00 PM	**Live Lecture** **Diabetes Remission – Review of Medical Evidence** Organiser: HKMA-New Territories West Community Network; Speaker: Dr Enoch WU	Miss Antonia Lee Tel: 3108 2514 1 CME Point
7:00 PM	**HKFMS Foundation Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms Nancy CHAN Tel: 2527 8898
27 TUE 7:00 PM	**Certificate Course on Lower Urinary Tract Symptoms 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr YU Cheong	Ms Vienna LAM Tel: 2527 8898
28 WED 7:00 PM	**Certificate Course on Wilderness Medicine 2021 (Video lectures)** Organiser: The Federation of Medical Societies of Hong Kong Speaker: Dr LAM Kam-leung	Ms Vienna LAM Tel: 2527 8898
29 THU 2:00 PM	**Live Lecture** **Update in Management of Lung Cancer** Organiser: HKMA-Hong Kong East Community Network; Speaker: Dr CHOY Tim-shing;	Ms. Candice Tong Tel: 3108 2513 1 CME Point

Answers to Radiology Quiz

Answers:

1. There is a hyperdense mass at the right suprasellar region with peripheral calcified foci.

2. The top differential to be considered is the right MCA giant aneurysm due to the typical location and presence of a calcified rim, usually seen in an aneurysm wall. Other differentials include meningioma and less likely neurogenic tumour and parasellar pituitary macroadenoma.

3. Urgent referral for contrast CT cerebral angiogram to look for right MCA giant aneurysm is suggested.

Dr LAU Hoi-to
MBBS, FRCR

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References:
1. Scicchitano R et al. Curr Med Res Opin 2004; 20(9): 1403-18. **2.** Kuna P et al. Int J Clin Pract 2007 May; (61)5:725-36. **3.** Bousquet J et al. Respir Med 2007; 101: 2437-46. **4.** Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2019. https://www.ginaasthma.org. Accessed on 6 Jan 2020.

Presentation: Budesonide/Formoterol Turbuhaler. **Indications:** Regular treatment of asthma where combination therapy w/ inhaled corticosteroid & long-acting β-agonist is appropriate. **160/4.5 mcg & 320/9 mcg/dose Turbuhaler** Symptomatic treatment of COPD. **Dosage: Asthma 1) Symbicort maintenance therapy 80/4.5 mcg & 160/4.5 mcg Turbuhaler** Adult ≥ 18yr: 1-2 inhalations bd. Max 4 inhalations bd. Adolescent 12-17 yr: 1-2 inhalations bd. Childn ≥ 6yr: 80/4.5 mcg Turbuhaler 2 inhalations bd. **320/9 mcg Turbuhaler** Adult ≥ 18yr: 1 inhalation bd. Max: 2 inhalations bd. Adolescent 12-17 yr: 1 inhalation bd. **2) Symbicort maintenance and reliever therapy** Taken as regular maintenance treatment and as needed in response to symptoms is appropriate. **80/4.5 mcg & 160/4.5 mcg Turbuhaler** Adult and adolescent ≥12yr: Recommended maintenance dose is 1 inhalation bd or 2 inhalations in either the morning or evening. Some may need 2 inhalations bd. Patient should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. No more than 8 inhalations per day should be taken, however, total daily dose up to 12 inhalations could be used for a limited period. Symbicort maintenance and reliever therapy is not recommended for children. **COPD 160/4.5 mcg Turbuhaler** Adult: 2 inhalations bd **320/9 mcg/dose Turbuhaler** Adult: 1 inhalation bd. **Contraindications:** Hypersensitivity to the active substance(s) or to any of the excipients (lactose, which contains small amounts of milk proteins). **Precautions:** Used for the shortest duration of time required to achieve control of asthma symptoms and discontinue once asthma control is achieved; Only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications; Taper dose when discontinuing treatment; Thyrotoxicosis; Phaeochromocytoma; Diabetes mellitus; Untreated hypokalaemia; Hypertrophic obstructive cardiomyopathy; Idiopathic subvalvular aortic stenosis; Severe hypertension; Aneurysm or other severe cardiovascular disorders; Quiescent pulmonary TB; Fungal & viral infections in the airways; Patients should take Symbicort maintenance dose as prescribed even when asymptomatic. Symbicort as needed is not intended for regular prophylactic use, e.g. before exercise; If oropharyngeal thrush occurs, patients should rinse their mouth with water after inhalations; Pregnancy & lactation. **Interactions:** CYP3A4 potent inhibitors (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors), beta-blockers, quinidine, disopyramide, procainamide, phenothiazines, terfenadine, tricyclic antidepressants, levodopa, L-thyroxine, oxytocin, alcohol, anaesthesia, other beta-adrenergic drugs or anticholinergic drugs, digitalis glycosides, xanthine derivatives, corticosteroids and diuretics. **Undesirable effects:** (Common) Palpitations, Candida infections in the oropharynx, pneumonia in COPD patients, headache, tremor, mild irritation in the throat, coughing, hoarseness. **Full local prescribing information is available upon request.**
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(Video Lectures)

Jointly organised by

The Federation of Medical Societies of Hong Kong

Hong Kong Society for Ultrasound in Medicine

The Obstetrical and Gynaecological Society of Hong Kong

Objectives:

1) To improve and update the knowledge and skills on obstetric ultrasonography of fetal anomalies
2) To improve and update the counseling on fetal anomalies
3) To update the ultrasonography of first trimester complications

Date	Topics	Speakers
26 May, 2021	The role of ultrasound in the era of NIPT	Dr. Wing-cheong LEUNG Consultant Obstetrician & Chief-of-service, Department of O&G, Kwong Wah Hospital
2 June, 2021	Ultrasonography of first-trimester complications	Dr. Charleen Sze-yan CHEUNG Associate Consultant Obstetrics & Gynaecology Queen Mary Hospital
9 June, 2021	Routine Mid-trimester morphology scan and common anomalies	Dr. Tak-yuen FUNG Chief of Service Obstetrics & Gynecology Hong Kong Baptist Hospital
16 June, 2021	Detailed second- and third- trimester diagnostic obstetric ultrasound examination and new ultrasound technology	Dr. Kwok-Yin LEUNG President, Hong Kong Society for Ultrasound in Medicine
23 June, 2021	Ultrasonography of the fetal heart: from basic to advanced examination	Dr. Ben Chong-pun CHAN Private Obstetrician
30 June, 2021	Ultrasonography of fetal gastrointestinal and genito-urinary anomalies	Dr. Amelia Pui-wah HUI Consultant Obstetrics & Gynaecology Queen Mary Hospital

Date : 26 May & 2, 9, 16, 23, 30 June, 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)
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)
Enrollment Deadline : 18 May 2021
Enquiry : Tel.: 2527 8898 Fax : 2865 0345 Email : vienna.lam@fmshk.org

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References: 1. NORVASC (amlodipine besylate) Prescribing Information. Pfizer Upjohn Hong Kong Limited; Version December 2018. **2.** IQVIA MIDAS MAT 202001, [C06 – Calcium Antagonist]. **3.** Williams B, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*.2018;39:3021-3104.

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(Hong Kong Branch)

Advance in Therapeutics Course 2021

Online/Onsite*

Date : 3rd May - 31st May 2021 (Every Monday Evening)
Time : Registration 6:45pm; Lecture: 7:15pm - 9:15pm
Option 1 : Online Lectures - Zoom
Option 2 : *Onsite Lectures (pending COVID situation & limited seats available)
Venue: Asia Medical Specialists, 8/F China Building, 29th Queen's Road Central, Hong Kong

3 May - Vaccines & Allergy

- **Vaccine Allergy: Myth & Truth**
  Dr. Gilbert CHUA
  Specialist in Paediatrics
  Chairman - Dr. Adrian WU, Vice President, BMA (HK)
- **Management of Co-Morbid Allergic Diseases**
  Dr. Alson Wai Ming CHAN
  Specialist in Paediatric Immunology, Allergy & Infectious Diseases

10 May - Body & Mind

- **Update on Diagnosis and Management of Migraine**
  Dr. Terence Mang Ho YUEN
  Specialist in Neurology
  Chairman - Dr Alex HUI, Council Member, BMA (HK)
- **Latest Treatment Recommendation on Eczema**
  Dr. Kwun Cheung HAU
  Specialist in Dermatology

17 May - Cancer: Treatment & Diagnostics

- **Management of Immunotherapy Toxicities**
  Dr. Conrad Chi Yan LEE
  Specialist in Clinical Oncology
  Chairman - Dr. Siu Kie AU, Specialist in Clinical Oncology
- **PET CT: Indications and Interpretations in Cancer Imaging**
  Dr. Benz Chi Ping WONG
  Specialist in Nuclear Medicine

24 May - Diabesity

- **Behold the New Cardiac Drug: SGLT2 Inhibitors**
  Dr. Adrian Yan Yue CHEONG
  Specialist in Cardiology
  Chairman - Prof. Brian TOMLINSON, Council Member, BMA(HK)
- **Update on Drug Treatment of Diabesity**
  Dr. Enoch WU
  Specialist in Endocrinology, Diabetes & Metabolism

31 May - Care for Advanced Diseases

- **Update on Oncological Treatment of Advanced Gastrointestinal Cancers**
  Dr. Stephan Lam CHAN
  Specialist in Medical Oncology
  Chairman - Dr. Raymond LO, President, BMA (HK)
- **Update on Treatment of Cancer Pain with Alternative Opioids**
  Dr. Penelope SHAM
  Specialist in Anaesthesiology

Places limited. Register early.

Course Fee: Free for BMA paid-up members with annual fees of $350 and course fee waived
For non-members: $200 onsite / online for 1 evening ; $450 onsite / online for all 5 evenings

Online Registration: http://bit.ly/3cKA3jy

Enquiries:
The Federation of Medical Societies of Hong Kong,
Tel. : 2527 8898 Fax : 2865 0345 Email : jovan.chun@fmshk.org

Zoom link to be sent after registration
Programme and arrangement may be subject to change with any unforeseen circumstances

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BRITISH MEDICAL ASSOCIATION
HONG KONG BRANCH

British Medical Association (Hong Kong Branch)
Advance in Therapeutics Course 2021 – *Online/Onsite**
All Doctors Are Welcome!

Please indicate your preferred way of participation by putting a tick "✓"in the appropriate box:

Date	Theme	Lecture	Online (Zoom)	*Onsite (pending COVID situation)
3 May	Vaccines & Allergy	➢ Vaccine Allergy: Myth & Truth ➢ Management of Co-Morbid Allergic Diseases		
10 May	Body & Mind	➢ Update on Diagnosis and Management of Migraine ➢ Latest Treatment Recommendation on Eczema		
17 May	Cancer: Treatment & Diagnostics	➢ Management of Immunotherapy Toxicities ➢ PET CT: Indications and Interpretations in Cancer Imaging		
24 May	Diabesity	➢ Behold the New Cardiac Drug: SGLT2 Inhibitors ➢ Update on Drug Treatment of Diabesity		
31 May	Care for Advanced Diseases	➢ Update on Oncological Treatment of Advanced Gastrointestinal Cancers ➢ Update on Treatment of Cancer Pain with Alternative Opioids		

☐Prof. ☐Dr. ☐Mr. ☐Mrs. ☐Ms. Last Name: _____ First Name: _____

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Please insert "✓" as appropriate:

- For BMA members:
  - ☐ I am a paid-up member and would like to attend the course FREE
  - ☐ I am a non paid-up member. I would renew my membership and attend the course FREE (membership fee HK$350).
- For non-BMA members
  - ☐ I am a non-member and would like to attend

Registration Fee: HK$200 onsite/online for 1 evening ; HK$450 onsite/online for 5 evenings

1. Please make a crossed cheque payable to ***British Medical Association (HK Branch)***
2. Return your registration and cheque to the following address:

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