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Singapore sidesteps global cancer drug shortages

By Rajesh Kumar

Singapore has managed to steer clear of a chronic shortage of key chemotherapy drugs currently plaguing much of the developed world.

But experts are calling for an early warning system to guard against any ripple effect in the long run.

Among the drugs in short supply in the US are leucovorin for treating colorectal cancer, liposomal doxorubicin used in breast and ovarian cancer, sarcoma, and multiple myeloma, 5-fluorouracil used in colon cancer, bleomycin used for Hodgkin's lymphoma and testicular cancer, and cytarabine used for leukemia.

The European Hematology Association and Cancer Council Australia have reported similar shortages, compelling clinicians there to switch drug regimens, substitute drugs, delay treatment and omit or reduce doses.

In Singapore and wider Asia, no such shortage has been felt so far. In rare cases where supplies of certain drugs do get delayed, the pharmaceutical companies have made stop gap arrangements wherein clinicians can borrow essential chemotherapy drugs from public hospitals, said private practitioner Dr. Wong Chiung

Ing, specialist in medical oncology at The Cancer Centre, Singapore.

Assistant Professor Lita Chew, head of oncology pharmacy at the National Cancer Centre Singapore (NCCS), said a sizable portion of chemotherapy drugs at NCCS are purchased through the Group Procurement Office.

"We have running contracts and projected deliveries that have served us well," Chew said. "For supplies that we purchased on our own, we work closely with our suppliers to pre-empt disruption and manage supply to patients."

The American Society of Clinical Oncology (ASCO) recently reported the findings of a survey of 214 US oncologists and hematologists which found that 83 percent of them were unable to prescribe their top choice chemotherapy agent, 94 percent reported shortages affecting patient care.

"Unfortunately, cancer drug shortages will likely be a persistent issue," said lead researcher Dr. Keerthi Gogineni of the Abramson Cancer Center at the University of Pennsylvania in Philadelphia, Pennsylvania, US.

One reason for this East vs West disparity is that different set of manufacturers and suppliers are ap-

Potent painkillers from cobra venom



King cobra is one of the world's most venomous snakes that can kill a human in one bite. But its venom could become the basis for a new generation of potent painkillers. Professor Manjunatha Kini of the National University of Singapore, in collaboration with colleagues Professor P. Gopalakrishnakone and Professor Peter Wong, has isolated a protein from king cobra's venom that could yield a painkiller 20 to 200 times more potent than morphine. The venom lacks the addictive properties of opioid painkillers currently on the market, said Kini. The animal studies have been encouraging and Kini hopes to test the drug in humans within a couple of years.

PT

proved to supply in the two regions what are essentially generic chemotherapy drugs. And Asian companies have enough capacity to meet local demand.

Dr. Wong Seng Weng, medical director at The Cancer Centre, Singapore, said that should not make Asians complacent. If just a fraction of the Asian suppliers managed to meet the US FDA regulations to

supply there, the Asian pool could shrink considerably causing similar shortages here.

"We cannot take the situation for granted and think we will continue to be not affected by the global chemotherapy drugs shortage ... It will be good to have in place an advance warning system," said Wong. Cancer care physicians and pharmacists are keeping an eye on the situation.

PT

2,000 liters of illegal codeine syrup seized

By Rajesh Kumar

The Health Sciences Authority (HSA) and the Central Narcotics Bureau (CNB) in a joint operation have smashed a codeine cartel, seizing almost 2,000 liters of illegal codeine syrup estimated to be worth S\$1.25 million in street value.

The culmination of the three-month long operation has taken the tally of such seizures of the pharmacy only medicine to a whopping 9,000 liters over the past three years.

"The [cumulative] figures include offenses such as illegal sale and importation of codeine cough mixtures and the [consignments] seized thus far were from various

locations within and outside of Singapore," said an HSA spokesperson, without disclosing specific locations.

The operation is being described as one of the biggest such crackdowns targeting suspected codeine smuggling syndicates. Four Singaporean men were arrested in the operation and are currently assisting HSA with investigations.

To date, 22 individuals have been prosecuted under the Poisons Act. Many of these offenders were apparently sourcing the syrup through legitimate suppliers, only to divert them to the black market. The HSA in 2009 imposed new controls on license holders who wish to export

cough mixtures from Singapore, whereby they are now required to obtain HSA's prior approval.

Meanwhile, codeine syndicates continue to use ingenious ways to

“Over the past three years, a whopping 9,000 litres of codeine syrup has been seized

smuggle in codeine syrup. The latest case was first detected by the Immigration & Checkpoints Authority (ICA) officers at Keppel Distripark on

28 March, wherein 3.8 liter canisters of the syrup were being smuggled in under guise of products such as tire shine, porcelain cleaners and degreasers.

Follow-up investigations by the HSA showed that the suspects brought the canisters to a residential unit and another rented storage facility, where they were processed and repackaged into smaller quantities, before being distributed to the black market.

"Codeine cough syrups should only be dispensed for medical use by licensed pharmacists or doctors. If used improperly and illegally, these can lead to serious health consequences," said Associate Profes-

sor Chan Cheng Leng, HSA deputy group director of the health products regulation group.

In addition to substance dependence as well as nausea, vomiting, constipation and confusion, codeine may also cause hallucinations, decreased heart rate and breathing, leading to coma and death if taken in excess, said Chan.

In a statement issued recently, the HSA said it will continue to step up its enforcement efforts against such offenses. Under the Poisons Act, anyone caught importing, selling or possessing products containing codeine without a license can be fined up to \$10,000 or jailed up to 2 years or both.

PT

Promote safe medication use beyond practice settings

Based on a speech by Minister of State for Health, Dr. Amy Khor, delivered at the Singapore Pharmacy Council Pharmacist's Pledge Affirmation Ceremony for 2013.



Dr. Amy Khor

As medication experts, pharmacists add value to the healthcare system through reducing medication-related problems and preventable adverse drug events. Such value-added services include medication reviews and medica-

tion reconciliation, managing patients in ambulatory clinics and actively collaborating in inter-professional teams to manage specific medication-related issues.

You should continue to work closely with each other and with other healthcare professionals to promote safe and effective medication use beyond your practice settings. In doing so, the profession will be aligned with, and be able to positively support, MOH's

"Healthcare 2020" vision towards improving accessibility, quality and affordability of health care to meet the needs of our population.

"I wish to acknowledge the efforts and contributions of pharmacist preceptors and mentors"

Earlier this year, the MOH formed a Healthy Living Master Plan Taskforce to develop a plan to encourage healthier living. As pharmacists, you are well-positioned to engage patients and to provide public education about healthy living and preventive care, such as by encouraging lifestyle modifications, early screening for diseases and helping patients improve medication adherence as part of chronic disease management.

As part of "Healthcare 2020", the MOH has made a commitment to develop the healthcare workforce to meet the needs of the population. In addition to building capacity and growing the numbers of healthcare professionals, we also need to ensure that we are developing a quality healthcare workforce.

The ministry will continue to invest in the training of all our healthcare professionals by providing funding to our institutions in the current financial year to enhance their capacity to deliver good quality clinical training.

In addition to classroom training within educational institutions, healthcare professionals, such as pharmacists, also undergo supervised training in the healthcare institutions. Such training would not be possible without a very important group of people: the pharmacy seniors and colleagues who serve as preceptors and mentors to guide the new graduates in the transition between university and the working world.

PharmacyToday

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Pharmacy Today is published 6 times a year by MIMS Pte Ltd. Pharmacy Today is on controlled circulation publication to pharmacists in Singapore. It is also available on subscription to members of allied professions. The price per annum is US\$48 (surface mail) and US\$60 (overseas airmail); back issues at US\$5 per copy. Editorial matter published herein has been prepared by professional editorial staff. Articles ending with PTNZ have been adapted from Pharmacy Today New Zealand. Views expressed are not necessarily those of MIMS Pte Ltd. Although great effort has been made in compiling and checking the information given in this publication to ensure that it is accurate, the authors, the publisher and their agents shall not be responsible or in any way liable for the continued currency of the information or for any errors, omissions or inaccuracies in this publication whether arising from negligence or otherwise howsoever, or for any consequences arising therefrom. The inclusion or exclusion of any product does not mean that the publisher advocates or rejects its use either generally or in any particular field or fields. The information contained within should not be relied upon solely for final treatment decisions.

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Printed by KHL Printing Co Pte Ltd, 57 Loyang Drive, Singapore 508968

PP17931/12/2013(033147) ISSN 1170-1927

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I wish to acknowledge the efforts and contributions of pharmacist preceptors and mentors to the development of Singapore's quality healthcare workforce. I hope the newly registered pharmacists will too embrace their future role as preceptors and mentors for the next generation of pharmacists and future colleagues. **PT**

Pilates a possible pain management tool

By Radha Chitale

Patients with chronic pain may be wary of exercise but some forms of movement, such as clinical Pilates, can alleviate symptoms and improve patient conditions in the long term, according to Ms. Irene Toh, a physiotherapist at Singapore General Hospital, Singapore.

Pilates can be effective for a variety of chronic pain conditions such as chronic lower back pain, whiplash injuries, fibromyalgia, chronic fatigue syndrome and arthritis.

Patients with chronic pain are unique because normal pain-modulating processes and endogenous analgesics that are triggered with exercise are not accessible to them.

In addition, Toh said chronic pain patients have an altered perception of their body because of their pain. When asked to describe affected areas they will often refer to them as disproportionately damaged or negative compared with unaffected areas. This perception

results in exaggerated sensitization, pain and poor movement control, and the resulting negative feedback can dissuade patients from exercising.

"The focus of Pilates is on good-quality movement and relaxed breathing," Toh said. "We have the ability to analyze movement and break it down for them to start thinking of the pieces... Once they see how to do it, they can put it into practice even when they are not in sessions."

Pilates was developed in Germany by a man named Joseph Pilates in the early 20th century and at the time it was also called control-gogy because of its focus on the mind to control muscles.

Clinical Pilates is a subset of Pilates developed in the 1990s. Together with mainstream physiotherapy techniques, clinical Pilates is especially good for rehabilitation for patients with musculoskeletal and neurological conditions because it aims to retrain faulty movement pat-

terns and improve movement efficiency and spinal stability.

The six principles of clinical Pilates are controlled movements, focus on proper form, developing core muscle stability, breathing, flowing movement and precision.

"I want patients to work smarter, not harder," Toh said. "When I progress the patient, I will increase the complexity of movement, not the amount or weight or resistance."

Research has shown that clinical Pilates is just as effective as regular exercise for improving disability, pain, function and health-related quality of life.

One study of patients with lower back pain showed that all participants, who had been randomized to 6 weeks of Pilates (n=44) or general exercise (n=43), improved significantly and similarly after 12 and 24 weeks, respectively, of follow-up. [*Med Sci Sports Exerc* 2012;44:1197-1205]

Simplicity of instruction and movement



Clinical Pilates can be effective for treating a variety of chronic pain conditions.

coupled with tactile and visual feedback should help reluctant patients begin to exercise more, Toh said, which can begin to alleviate their chronic pain. **PT**

New Panadol formulation rolled out



GSK marketing head Mr. Ashish Joshi, Chelsea Clinic GP Dr. Charlotte Yung and GSK-Singapore general manager (consumer healthcare unit) Mr. Lee Hon Tong, formally launching the new Panadol Cough & Cold 2-in-1 caplet.

A new combination caplet formulation of Panadol® – Panadol® Cough & Cold (GlaxoSmithKline) – has become available islandwide and is indicated for the symptomatic relief of chesty cough and cold symptoms in adults and children aged over 6. It contains paracetamol, phenylephrine hydrochloride and guaifenesin to relieve pain and reduce fever, ease nasal and sinus congestion and loosen phlegm for easy expectoration.

"Cold symptoms can be really irritating," said Dr. Charlotte Yung, family physician at the Chelsea Clinic. "People experience sneezing, runny or stuffy nose, coughing and generally feel unwell... There is no cure for common cold but combination medications can help control the symptoms and improve quality of life."

Yung said Singaporeans are particularly susceptible to catching colds due to various factors, primarily the high population density of the island's urban environment, and the large number of travelers coming in and out of the country. **PT**

Loratadine now available OTC



Loratadine (Claritin®, Merck Sharp & Dohme) is now available over the counter in Singapore. The non-drowsy antihistamine was approved for addition to Singapore's General Sales List (GSL), which lists drugs available for sale directly to consumers, in January 2012.

"Pharmacy sale of GSL medicines have shown to be safe, as pharmacists and trained healthcare assistants are on hand to counsel the patient on the medicines they are being supplied," said Ms. Ella Chan Tsui Pik, principal pharmacist, and Ms. Cassandra Chang Wee Ting, senior pharmacist at Singapore General Hospital.

"Having Claritin reclassified to GSL can provide easier access to patients in situations where it is not possible to obtain pharmacy-only medicine for the immediate use of short-term self-limiting conditions."

However, they added that patients who self-treat and purchase such medications outside of pharmacies could, among other possible issues, be mistaking their symptoms for other ailments. **PT**

Quit smoking medications are effective

Nicotine replacement therapies (NRTs) and other licensed drugs can indeed help people quit smoking, a systematic review has confirmed.

The overview of previous Cochrane reviews supports the use of the smoking cessation medications that are already widely licensed internationally, and shows that another drug licensed in Russia could hold potential as an effective and affordable treatment.

The findings serve as a reassurance to pharmacists and other health professionals involved in smoking cessation programs.

In most countries including the US and Europe, the only medications currently licensed for smoking cessation are NRTs such as nicotine patches and gums, the antidepressant bupropion and the drug varenicline, which blunts the effects of nicotine on nicotine receptors in the brain. In Russia and other parts of Eastern Europe, cytisine, similar to varenicline, is also licensed for smoking cessation.

The researchers combined the findings of existing Cochrane reviews on the subject, using all the available data from across individual reviews. In total, they collected evidence from 267 studies, which together involved a total of 101,804 people. The studies covered a wide variety of licensed and unlicensed smoking cessation medications, comparing the treatment with placebo, and the three main treatments with each other. If a person stopped smoking for 6 months or longer, this was considered a successful quit attempt.

The three widely licensed medications and cytisine all improved smokers' chances of quitting. The odds of quitting were about 80 percent higher with single NRT or bupropion than with placebo, and between two and three times higher with varenicline than with placebo. However, varenicline was about 50 percent more effective than any single formulation of NRT (patches, gum, sprays, lozenges and inhalers), but similar in efficacy to combining two types of NRT. Based on two recent trials, cytisine improved the chances of quitting nearly four-fold compared with placebo. Among other treatments tested, nortriptyline, another antidepressant drug, was more effective than placebo but did not offer any additional improvement when combined with NRT.

"This review provides strong evidence that the three main treatments, nicotine replacement therapy, bupropion and varenicline, can all help people to stop smoking," said lead researcher Dr. Kate Cahill of the department of primary care health sciences at the University of Oxford in Oxford, UK. "Although cytisine is not currently licensed for smoking cessation in most of the world, these data suggest it has potential as an effective and affordable therapy."

The researchers also assessed the safety of different medications. Bupropion, which is known to trigger occasional seizures in vulnerable people, did not lead to an increase in the rate of seizures when used for smoking cessation in its slow-release version. Overall, NRT, bupropion and varenicline are considered low risk treatments, although the researchers say the results are currently less clear-cut for varenicline.

"Further research may be warranted into the safety of varenicline," said Cahill. "However, in the trials we looked at we did not detect evidence of any increase in neuropsychiatric, heart or circulatory problems." **PT**



HSA cracks down on illegal online pharmacies



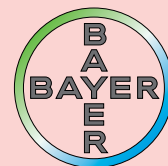
Singapore's Health Sciences Authority (HSA) has confiscated over 25,000 units of illegal health products, including four brands of slimming products laced with a prohibited substance, during a global operation targeting illegal online pharmacies.

The seized products, worth \$10,000, had been on sale on 40 websites and posts. Also seized were counterfeit cosmetic products and substandard medical devices. At least four persons have been held for questioning.

The slimming products, namely VTOX Trim Up, Bonjour, CURVY Pearl beauty slimming orange juice and V12 Fruit Slimming, were found to contain sibutramine, a potent medicine for weight loss but its sale was suspended in Singapore in October 2010 due to increased risk of serious cardiovascular events such as stroke or heart attack.

Other adverse events associated with sibutramine include hallucination, anxiety, dry mouth and constipation. All four slimming products claimed to contain 100 percent natural ingredients and guaranteed to deliver immediate results without side effects.

The week-long crackdown was part of Operation Pangea, a global cooperative effort to combat the illegal online sale and distribution of counterfeit and adulterated medicines and bring perpetrators to justice. The operation started in the UK and has since grown to include over 100 countries, resulting in the arrest of 58 persons and the seizure of US\$41 million worth of illegal medicines worldwide. This year, 9,600 illegal online pharmacies have been identified and shutdown. **PT**



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Feature



Helping women treat vaginal yeast infection

By Laura Dobberstein

Yeast infection is a common fungal infection that can strike in many areas of the body, including the mouth and even nipples. It can, however, be of particular discomfort when it appears vaginally.

As many as three out of four women will experience vaginal yeast infections, also called vaginal thrush or candidiasis, at some point and many will experience the condition multiple times during the course of their life, according to the US-based Mayo Clinic.

The condition is caused by an overgrowth of a yeast-like fungus called *Candida*. Many healthy women have *Candida* in their vagina and do not experience problems because "good" bacteria such as *Lactobacillus acidophilus* keep the yeast under control. When the balance between the 'good' and the harmful bacteria is disturbed, yeast can grow too fast and cause irritation of the vagina and vulva.

Symptoms

Symptoms of thrush can vary but often include itching in the infected area, vaginal discharge that may have an unpleasant odor, burning during urination, discomfort during intercourse and abnormal growth around the vagina, according to Dr. Lubna Harharah of The Obstetrics & Gynaecology Centre, a subsidiary of the Singapore Medical Group.

Women who are pregnant, obese, diabetic, take hormonal birth control or have a weakened immune system are particularly susceptible to vaginal yeast infections. Excessive douching or recent antibiotic treatments

can increase the risk as these activities eliminate or reduce the "good" bacteria in the vagina.

The infection is sometimes passed between sexual partners, although vaginal yeast infections are not considered a sexually transmitted disease.

Diagnosis and treatment

During a typical examination for vaginal yeast infection, a doctor will conduct a pelvic exam to look for redness, swelling and discharge, explained Lubna. A swab may be used to take a sample of vaginal fluids for microscope or laboratory analysis.

Pharmacists can recommend over the counter (OTC) ointments and creams for uncomplicated cases of vaginal yeast infection. A single dose oral pill is also available with a doctor's prescription. A patient with recurrent or difficult to treat vaginal yeast infections and pregnant women with the condition should consult with their doctor.

Jury still out on probiotics

Many patients are turning to probiotic supplementation as a treatment. Probiotics contain live microbial organisms and can be taken in pill form or as a food. For example, yogurt that contains live active cultures of *Lactobacillus acidophilus* may help control *Candida* overgrowth. However, probiotics are not an approved treatment for vaginal yeast infection.

"At this point, researchers are studying whether probiotics help prevent or fight infections in the vagina," said Lubna. "A few studies

have hinted that probiotic [supplementation] might improve health, but scientists say there is not enough proof to be sure."

Pharmacy's role

Pharmacists can play a vital role in helping patients get adequate treatment for the condition. They can help patients understand that:

- Patients should only self diagnose this condition if they have had a prior, physician-diagnosed vaginal yeast infection and feel comfortable recognizing the signs and symptoms.

“ Symptoms often include itching, discharge, unpleasant odor, burning during urination ...

- Those exhibiting fever, nausea, chills, vomiting, rash, lower abdominal pain, back pain, strong smelling discharge, or pain in shoulder, pregnant women and children under the age of 12 with complaints of vaginal yeast infection should consult with a doctor.
- OTC medication for vaginal yeast infection is available as 1-day, 3-day and 7-day treatments. Symptoms are generally absent by the end of 7-day treatment. Patients undergoing 1-day and 3-day therapy may not see results for a few days after treatment. The patient should consult with their doctor if

symptoms persist for longer than 7 days following the first day of treatment.

- Treatments inserted into the vagina should be applied at night to reduce the change of accidental leakage of the cream. While the treatments do not stain, the patient may wish to wear a sanitary pad to protect clothing.
- Women who begin their menstrual flow should continue any vaginally inserted treatment as usual, but should avoid using tampons as they may absorb the antifungal substance and make the medication less effective.
- Any reusable applicators should be washed and dried thoroughly after use to prevent the growth of organisms.
- Douching, intercourse, spermicides and any other vaginal product should be avoided during cream or ointment treatment for vaginal yeast infection. Vaginal antifungal products may also damage latex contraceptives.
- Patients with less than 2 months since their previous vaginal yeast infection should consult with their doctor. Recurrent yeast infections may be a sign of other conditions such as diabetes, pregnancy, HIV and immunodeficiency disease.

When it comes to treatment, all available medications are considered effective and patient satisfaction often depends on past experience. A pharmacist may want to ask the woman which methods have worked for her in the past to help her select an option that will put her on the road to relief and better health.



Ms. Ong Wan Chee is one of the pharmacists who operate SGH's Medication Management Service. She helps patients understand the drugs they have to take.

Getting the right dose of the right drugs

Pharmacists play a bigger role in helping patients manage their medication.

The patient's case was perplexing. He had enough diabetes medicine to last him for more than 6 months, even though pharmacies do not normally dispense more than 3 months' worth of medication.

After many questions, the pharmacist found out that the 69-year-old forgot to take his medication.

"The pharmacist realized that the patient just kept collecting the medicine after every visit to his doctor,"

said Ms. Ong Wan Chee, pharmacist at Singapore General Hospital (SGH). "He did not understand what medication he had to take, and he also did not take the amount that he was prescribed."

Unsurprisingly, his test results showed that his diabetes was not under control. He also suffered from long-term hypertension and had fluctuating blood pressure levels.

Such cases often arise when pa-

tients take many different kinds of medicine for a variety of diseases. There are also patients who see various doctors for different complaints, but end up being given similar drugs.

To help patients like the old man, SGH started a Medication Management Service last year. The service is operated by pharmacists who make sure that patients understand how to take their medicine.

The pharmacists review the pa-

tients' medication to ensure they have not been prescribed duplicate drugs, and also check for the possibility of adverse reactions between the drugs. In the case of the 69-year-old diabetes patient, he was given a chart prepared by his pharmacist to document his blood sugar levels. The pharmacist explained the medication he had to take and taught him to monitor his blood pressure.

After the consultation, the patient's blood sugar levels improved. This allowed his doctor to adjust the dosage of his medication. A few months later, the patient's diabetes was under control and he no longer faced the risks that required the attention of an acute-care hospital.

Better care for patients

The case is a good example of how pharmacists can contribute to better care for patients, said Ms. Ong. Pharmacists are often seen as people who passively dispense medicine. In reality, they are trained to do a lot more. They are qualified to counsel and educate patients and to help them take charge of their health.

The Medication Management Service thus allows pharmacists to play a bigger role. For example, when a patient does not tell his doctor that he has not been taking his medication, there is a risk that he would be asked to take a higher dose because his doctor may think that his condition is worsening.

"So, we try to establish a relationship with the patients," said Ms. Ong. "We want them to feel comfortable enough to tell us why they're not taking their medication."

When patients gain a better understanding of the drugs they are taking, they are better able to manage their diseases. And this could help to reduce the number of people admitted to hospital for medication-related problems.

A recent review of SGH renal transplant patients found that 40 out of 100 were not taking their medication correctly. Some were not taking their medication, while others took less than their prescribed dose. The study, carried out between January and May last year, also showed that 12 percent of the patients had adverse reactions to their medication.

Courtesy: Singapore Health

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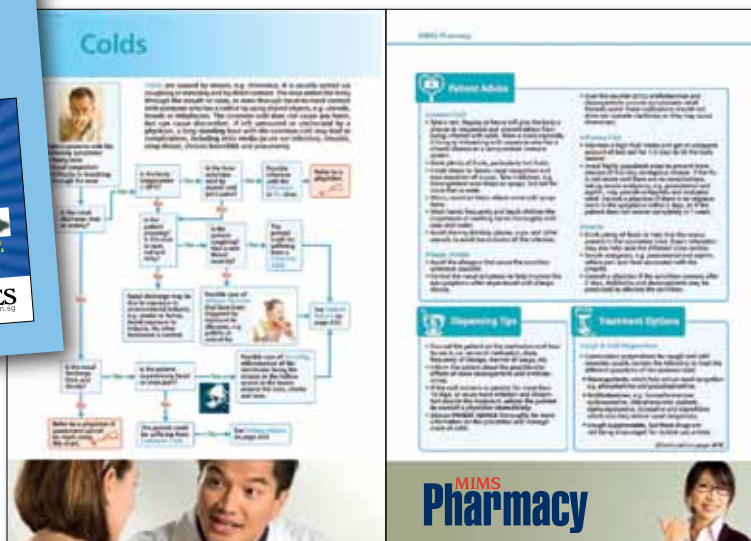
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Business

Watsons on expansion spree

By Rajesh Kumar

Health and beauty retailer Watsons is expanding its portfolio by opening up to six new stores this year.

With the recent addition of one of its largest stores at JEM [Jurong East Mall], the company boasts of 112 stores islandwide and competes with Guardian's 150 stores in what is becoming a crowded market.

"To differentiate ourselves from the industry, we will continue to add value-added health services to bring more to our customers," said Watsons Singapore Chief Operating Officer Mr. Daniel Teo, while explaining his strategy to deal with the competitive pressures.

In addition to providing general pharmacy services, the company has tied up with Fullerton Healthcare Group to provide discounts on health screening packages for its loyalty card members and discounts for senior citizens.

In June this year, naturopath services were added at select stores, including Watsons Paragon. "By pairing pharmacy services with na-

turopathy, we hope to provide a more holistic health service to customers," said Teo.

Although Singapore's health and beauty retail market is booming – it grew by 5 per cent to reach S\$3.3 billion last year, according to Euromonitor – the margins are eroding due to rising costs. This has prompted retail businesses to come up with newer ways to compete for the customer dollar.

At Watsons, interactive retail spaces and concepts are being added for what Teo calls enhancing customers' shopping experience. These include JBeautyLand, the brand's first-ever exclusive Japanese beauty counter, and Beautilicious, a segment showcasing the latest and exclusive oral beauty supplements.

Teo said Watsons soon plans to roll out the Baby & Wellness corner, trialed at the flagship Takashimaya store last year, to more stores that are catering to young families. The corners will provide more information on-shelf to help parents select the best baby wellness items and will have pharmacists and pharmacy technicians on hand to provide expert advice and service.



A recent Applied Survey Data Analysis (ASDA) revealed that more men are investing in their appearance, with one in eight men spending at least 1 hour every day on grooming alone.

Taking a cue, the company has developed a Men's Corner designed to offer the latest skincare, personal and grooming items just for men, with a hope that all that extra effort will eventually raise profitability. **PT**

Covance expands Singapore lab



The drug development services provider Covance has expanded its facility in Singapore to respond to the current and future growth of drug development in the Asia Pacific region.

The company's 2,700-square meter laboratory is the largest of its kind in Singapore, providing clinical testing services to clients in Asia, including South Korea, Taiwan, Hong Kong, the Philippines, Australia, and India.

The expansion doubles the size of the company's genomics footprint in Singapore, while also adding capabilities in anatomic pathology and nutritional chemistry. The facility provides services including chemistry, immunology, hematology, flow cytometry, genomics, anatomic

pathology, and microbiology, and has similar laboratories in Indianapolis, Indiana (US); Geneva, Switzerland; Shanghai, China; and Tokyo, Japan.

"Covance has helped pharmaceutical and biotech companies develop one-third of all prescription medicines in the market today," said Mr. Jon Koch, the company's corporate vice president and global general manager for central laboratory services.

"This expansion will help us better serve both our local and multinational customers' R&D needs in key therapeutic areas like oncology and metabolic diseases while reflecting Covance's continued commitment to the Asia Pacific region." **PT**

Russian firm to buy Singapore drug company

Russia's biggest pharmaceutical company Pharmstandard has offered to acquire Singapore's little known Bever Pharmaceutical, for US\$630 million by the end of this year, and fold Bever into its own branded OTC medicines unit that is being spun off.

The acquisition is subject to approval by the company's shareholders at its extraordinary shareholder meeting scheduled for 17 August. The new entity will be more profitable through a likely foothold in the

lucrative Asian market, and will give Pharmstandard an opportunity to focus on its profitable prescription drugs business, according to industry reports.

Bever is believed to be affiliated with one of Pharmstandard's board members and is involved in the sale of active pharmaceutical ingredients. Earlier this year, the company gained the rights to sell Pharmstandard's anti-flu medicine Arbidol and non-sedating anxiolytic, Afobazol. **PT**

Bio-Oil best-selling scar, stretch mark product

Bio-Oil, a specialist skin product manufactured in South Africa, was recently ranked the top-selling scar and stretch mark product in Singapore by Nielsen, a leading global information and insights company.

Mr. Andre van Straten, Counsellor (Political), South African High Commission, congratulated Bio-Oil division manager for Singapore and Malaysia Ms. Low Hooi Wan (pictured) on the brand's achievement.

Bio-Oil contains purcellin oil, vitamins A & E, and natural plant oils such as lavender, calendula, rosemary and chamomile that help improve the appearance of scars, stretch marks and uneven skin tone. **PT**



Drug Profile

Azilsartan medoxomil: Selective angiotensin II receptor blocker for the treatment of hypertension

Hypertension – a risk factor for cardiovascular and cerebrovascular disease – is a leading cause of premature death worldwide. This month, we profile azilsartan medoxomil, a relatively new anti-hypertensive agent which helps to reduce blood pressure by antagonizing the vasoconstrictor and aldosterone secreting effects of angiotensin II.

Naomi Adam, MSc (Med), Category 1 Accredited Education Provider (Royal Australian College of General Practitioners)

Introduction

In the South-East Asian region, 36 percent of adults (37.3 percent of men and 34.9 percent of women) have hypertension and the prevalence is increasing rapidly due to the aging population and the shift from agrarian lifestyle to modern urban life. [High blood pressure: Global and regional overview. WHO World Health Day 2013] Interestingly, while the prevalence of hypertension in Asia is similar to that globally, the patterns of death differ compared with Western nations. Hypertension and stroke occur at a relatively younger age in Asians, and high proportions of deaths from cerebrovascular disease are due to hemorrhagic stroke. The reasons for these ethnic differences are not known. [*J Hum Hypertens* 2000;14:749-763, Hypertension in the Asian Pacific region: The problem and the solution. Workshop Report, Beijing, China, November 15, 2007]

Eight classes of medications are currently used in the treatment of hypertension. They include diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-adrenergic blockers, alpha-adrenergic blockers, calcium-channel blockers (CCBs), central alpha-adrenergic receptor agonists (also called central adrenergic inhibitors), and direct renin inhibitors (DRIs). Till recently, there were seven different ARBs available: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan. Azilsartan medoxomil is a new addition to the ARB class, which received FDA approval in February 2011. [*Drug Forecast* 2011;36:634-640]

Azilsartan medoxomil Pharmacology

Angiotensin II, a peptide hormone, is the major pressor agent in the renin-angiotensin system (RAS). Its effects include vasoconstriction, stimulation of the synthesis and release of aldosterone, cardiac stimulation and the renal reabsorption of sodium. [*Clin Drug Invest* 2012;32:621-639] Azilsartan is a selective blocker of the angiotensin II receptor that antagonizes the vasoconstrictor and aldosterone

secreting effects of angiotensin II, thereby reducing blood pressure (BP).

Azilsartan is a more potent blocker of the angiotensin II receptor than other ARBs, including telmisartan, olmesartan, irbesartan and valsartan. Furthermore, azilsartan dissociates from the angiotensin II receptor more slowly than the comparator ARBs. The variation in potency and receptor binding is due to structural differences between the drugs.

Pharmacokinetics

Azilsartan medoxomil is a prodrug that is hydrolyzed in the gastrointestinal tract to the active agent, azilsartan. Bioavailability of azilsartan is estimated to be 60 percent. Absorption is not affected by food and peak plasma concentrations are reached with 1.5 to 3 hours of dosing.

The primary route of metabolism of azilsartan is the liver enzyme cytochrome P450 2C9. Two main metabolites are formed, and neither of these has any appreciable biological activity. The elimination half-life of azilsartan is 11 hours; it is excreted in the feces (55 percent) and urine (42 percent), with 15 percent of the drug remaining unchanged.

Clinical efficacy

Seven double-blind, randomized clinical trials involving a total of 5,941 patients with hypertension provided the evidence base for registration of azilsartan medoxomil. The studies ranged in duration from 6 weeks to 6 months and the doses studied were 20 to 80 mg. An active-controlled comparison over 6 weeks showed that azilsartan medoxomil was more effective in lowering systolic BP than maximal doses of either valsartan or olmesartan, without an increase in adverse events. [*Hypertension* 2011;57:413-420] Similarly, a 24-week study found that azilsartan medoxomil 40 and 80 mg was associated with a significantly greater reduction in both clinic and mean 24-hour systolic BP more than ramipril 10 mg. [*J Hypertens* 2010;28(e-Suppl A):e283]

Azilsartan medoxomil has also been studied in combination with amlodipine 5 mg over 6 weeks. This study demonstrated that the combination of azilsartan medoxomil 40 or 80 mg with amlodipine 5 mg is efficacious in the treatment of stage 2 hypertension, and the addition of amlodipine may help to reduce the oc-



Seven RCTs involving nearly 6,000 patients with hypertension provided the evidence base for registration of azilsartan medoxomil.

currence of peripheral edema associated with azilsartan medoxomil. [*J Hypertens* 2010;28 (e-Suppl A):e279-e280] In practice, ARBs are frequently combined with thiazide diuretics.

“ The prevalence of hypertension in Asia is similar to that globally

One study evaluated the long-acting, thiazide-like diuretic chlorthalidone in combination with azilsartan medoxomil. The addition of the ARB to chlorthalidone resulted in significantly greater reductions in 24-hour systolic BP, compared with diuretic alone. [*J Clin Hypertens* 2010;12(Suppl 1):A114] Most commercially available fixed-dose combination tablets that contain an ARB plus thiazide diuretic utilize hydrochlorothiazide, despite evidence that chlorthalidone has a much longer half-life and can lower BP more effectively. In a 10-week study, azilsartan medoxomil (40 mg) was studied in combination with either chlorthalidone (12.5 mg) or hydrochlorothiazide (12.5 mg). The reduction in clinic systolic BP was significantly greater in the group receiving azilsartan medoxomil and chlorthalidone compared with

the group given azilsartan medoxomil and hydrochlorothiazide. Azilsartan medoxomil and chlorthalidone are now available as a fixed-dose combination in a single tablet – the only commercially available formulation of an ARB plus chlorthalidone.

Adverse effects

The tolerability of azilsartan medoxomil was generally good in three randomized controlled trials of up to 24 weeks duration. The most common side effects were headache and dizziness, although these and other treatment-emergent adverse events occurred at rates comparable with placebo.

Dosing

The recommended starting dose of azilsartan medoxomil is 40 mg once daily. If blood pressure response is insufficient, the dose may be titrated to 80 mg once daily. There are no data regarding use of azilsartan in severe renal impairment, so it must be used with caution in this setting. In mild or moderate renal impairment, no dose adjustment is required. There are no data in patients with hepatic impairment either. A lower starting dose is recommended in patients with liver diseases and the maximum of 80 mg should not be exceeded. **PT**

Treating nail psoriasis

By Laura Dobberstein

Monoclonal antibodies targeting tumor necrosis factor alpha (TNFa), such as infliximab and golimumab, superficial radiation therapy, grenz rays and electron beam are likely effective treatments for difficult-to-treat nail psoriasis, according to a Cochrane review of 18 studies.

"It is known that more severe psoriasis is associated with poorer quality of life," said study author Dr. Anna de Vries from the department of dermatology at the Academic Medical Center in Amsterdam, the Netherlands, and colleagues. [Cochrane Database Syst Rev 2013;1:CD007633]

"Half of those with psoriasis of the nails are limited in their profession, housekeeping and daily activi-

ties or both. More than 90 percent have cosmetic problems that cause social embarrassment... [and] over 50 percent suffer from pain due to nail changes."

Five out of the 18 randomized controlled trials examined by de Vries and team showed a significant improvement of nail psoriasis with topical, systemic and radiation treatments. Compared with placebo after 6 to 12 months of therapy, treatments containing infliximab im-

proved nails by more than 57 percent and systemic treatment golimumab improved nails by 33 to 54 percent, depending on dosage.

In one study, superficial radiotherapy improved nail condition by 20 percent compared with no change with placebo after 3 to 6 months.

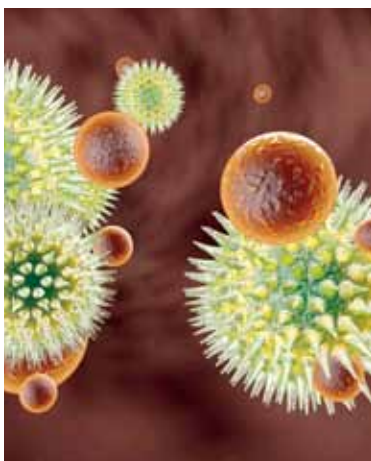
Although the trials reported treatment success, de Vries and team noted a need for more rigorous clinical trials. Systemic treatments were described as unrealistic due to

potentially dangerous side effects unless the condition was severe, refractory to other treatments or had a major impact on the patient's quality of life.

Most evidence supporting the effectiveness of topical treatment was considered inconclusive and of poor quality. The authors also noted that although radiation treatments were found to be beneficial, the treatment is not often utilized by medical professionals, the researchers said. **PT**



Enzyme acts as retroviral alarm



A particular enzyme, known as cyclic-GMP-AMP synthase (cGAS), acts as an immune sensor for HIV and other retroviruses, sounding the alarm at the first sign of infection, according to research. [Science Express, online first]

Despite enormous biomedical interest in retroviruses, the body's innate immune responses to them are still poorly understood, which in turn hampers vaccine development, said the researchers.

Sensors that are able to detect the presence of retroviruses in their hosts have so far been largely unknown. The researchers used primary human cells to show that the reverse transcription of HIV – a process needed for replication of the virus – causes cGAS to trigger an innate immune response against it, which involves the production of interferons. Cells lacking the enzyme were unable to detect HIV, SIV and murine leukemia virus (MLV), they said. This insight into the body's innate immune sensing of HIV may one day contribute to vaccine development. **PT**

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Watch out for abnormal heart rhythms with azithromycin: HSA

By Rajesh Kumar

The Health Sciences Authority (HSA) has advised GPs, pharmacists and other health professionals to be aware of the risk of abnormal heart rhythms when considering azithromycin as a treatment option for patients at risk for cardiovascular events.

Azithromycin is an azalide, a subclass of macrolide antibiotics derived from erythromycin that is widely used both orally and intravenously for the treatment of upper and lower respiratory tract infections, among others.

The advisory comes following evidence from two recent studies suggesting the drug can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm.

Patients at particular risk for developing this condition include those with known risk factors such as existing QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or use of certain drugs used to treat arrhythmias.

"HSA is currently working with the relevant product license holders to update the package inserts of all azithromycin products to strengthen the warnings regarding the risk," the April advisory said. The US FDA has already updated the package inserts in the US to strengthen the Warnings and Precautions section for the drug.

Currently, 17 azithromycin-containing products are registered in Singapore. Eleven of them are generics. Although closely related macrolide drugs such as erythromycin and clarithromycin are known to increase the risk of serious ventricular arrhythmias and are associated with an

increased risk of sudden cardiac death, azithromycin has previously been reported to be better tolerated than other macrolides, and has minimal side effects.

Two research studies recently provided evidence on the risk of QT prolongation associated with this drug. One study suggested a higher risk of cardiovascular deaths and deaths from any cause in persons treated with a 5-day course of azithromycin compared to persons treated with amoxicillin, ciprofloxacin, or no drug. [*N Engl J Med* 2012; 366:1881-1890]

“ HSA is currently working with the relevant product license holders to update the package inserts of all azithromycin products

"[However], there were some limitations to this study, such as potential bias due lack of randomization to the antibacterial drugs, outpatient setting investigation where it is likely that few patients were treated for severe or life-threatening infections, and the method of determination of cardiovascular deaths through death certificates instead of full medical records," the HSA said in its advisory.

Despite these, the study was noted to be methodologically sound and supportive of the validity of the overall findings.

The estimated excess risk of cardiovascular



death compared with amoxicillin varied considerably with the patients' baseline cardiovascular risk, from roughly 1 in 111,000 among healthier patients to 1 in 4,100 among high-risk patients. The duration of the elevated risk of all-cause mortality and of cardiovascular death corresponded to the duration of azithromycin therapy.

The HSA said increase in total deaths was determined to be attributed to cardiovascular deaths and not from other causes. The excess risk of cardiovascular death, especially of sudden death, was consistent with arrhythmias from drug-related QT prolongation.

The second randomized, placebo controlled parallel trial was conducted by a drug manufacturer to assess the effects of azithro-

mycin on the QT interval in 116 healthy adults. These subjects received either chloroquine (1000mg) alone or in combination with azithromycin (500mg, 1000mg, and 1500mg once daily). [<http://goo.gl/n2tst>]

Co-administration of azithromycin increased the QTc interval in a dose- and concentration dependent manner. In comparison to chloroquine alone, the maximum mean (95% CI) increases in QTcF were 5ms (10), 7ms (12) and 9ms (14) with the co-administration of 500mg, 1000mg and 1500mg azithromycin, respectively.

"Healthcare professionals are also encouraged to report all suspected adverse reactions associated with azithromycin to the vigilance branch of the HAS," the HSA said. **PT**

Traditional meds may help in diabetic nephropathy

By Rajesh Kumar

Limitations of current therapies have prompted significant basic and clinical interest in the use of traditional medicines for the treatment of diabetic nephropathy (DN).

Natural and traditional herbal medicines may potentially reverse kidney damage at the onset of proteinuria and may prove to be complementary, if not alternative, to the existing allopathic therapies, said Dr. Basil Roufogalis of the faculty of pharmacy at University of Sydney in Sydney, Australia.

Diabetic patients progressively develop clinically significant DN. Current therapy for this condition includes dietary protein restriction, blood pressure control, ACE inhibitors and angiotensin receptor blockers. However, a large number of patients still develop intractable disease, which is prompting the search of natural options, said Roufogalis.

Scores of randomized controlled trials involving traditional Chinese medicines such as ginkgo biloba, dogbane, astragalus, danshen and cordyceps mushroom; Ayurvedic medicines derived from fenugreek spice, curcumin (turmeric), ekanayaka and bark of the Arjuna tree and western herbal medicines based on milk thistle, north American ginseng, haw-

thorn and mango have shown different modes of action imparting nephro protection and reversing damage through up- or down-regulation of various molecular mechanisms.

Fenugreek, for instance, is believed to restore kidney function through decreased activities of superoxide dismutase (SOD) and catalase, increased concentrations of malon-

“ Natural and traditional herbal medicines may prove to be complementary, if not alternative, to the existing allopathic therapies

ndialdehyde in the serum and kidney, and increased levels of 8-hydroxy-2'-deoxy-guanosine in urine and renal cortex DNA. Ginkgo biloba extract has shown to decrease blood and plasma viscosity in patients with early DN.

Dogbane is believed to have protective effects on renal function through the inhibition of renal cortex SOD and glutathione activity while Arjuna bark is believed to cause significant reduction in lipid peroxidation, increased



Various traditional Chinese, Indian and western herbal medicines have been shown to impart nephro-protection.

superoxide dismutase, catalase, glutathione peroxide etc in clinical trials.

However, some of these trials suffered from poor methodological quality and lack of blinding while others were in rats, said Roufo-

galis. That is why long-term, double-blinded randomized controlled trials with large human sample sizes involving such medicines need to be conducted to provide stronger clinical evidence, he added. **PT**



The Science of Flavors in Food

By Radha Chitale

The harmony of a delicious meal is often called a labor of love, but it is also the evolutionary product of history, culture and good chemistry.

Chefs and scientists have long tried to describe the underlying patterns of tasty dishes. Within the last decade, a theory of flavor pairings has emerged stating that ingredients sharing flavor compounds are more likely to taste good together than ingredients that don't, which can lead to unexpected combinations.

For example, analysis of shared compounds landed white chocolate and caviar together on upscale menus around the world – the two shared the 'fishy' chemical trimethylamine, among others.

But new research using flavor networks has shown that the food pairing principle is both true and not true, and is significantly linked to region.

Such studies expand scientific understanding about what tastes good. Harnessing patterns in how people combine foods could help develop new products that benefit health without compromising the palate.

An amateur interest in molecular gastronomy led Dr. Sebastian Ahnert, a fellow in the Theory of Condensed Matter Group of the Cavendish Laboratory at University of Cambridge in the UK, to apply the theory of complex networks to flavor compounds, one of the basic components of flavor, besides odor and freshness, to uncover the patterns behind how people combine ingredients.

Ahnert and colleagues at Harvard University and Indiana University in the US mined 56,498 recipes from the US recipe database sites **Allrecipes.com** and **Epicurious.com** and the Korea-based site **menu-pan.com** to compile a list of 381 basic ingredients and 1,021 flavor compounds found in them. [*Sci Rep* 2011;1:196. Epub 2011 Dec 15]

Statistical analysis yielded a bipartite flavor network that shows the connectedness of any two ingredients based on how many flavor compounds they share.

For example, fruits are connected to each other and share many flavor compounds with wine and tea, while mushrooms inhabit a flavor island of their own.

But when the researchers grouped the ingredients by cuisine, the principle of flavor pairing proved to be untrue for Asian food.

"In North American [and Western European] recipes, the more compounds are shared by two ingredients, the more likely they appear in recipes. By contrast, in East Asian cuisine the more flavor compounds two ingredients share, the less likely they are to be used together," they said.

The researchers found that the iconic harmony or dissonance, respectively, of the regional foodscape is dominated by ingredients

including milk, butter, cocoa, vanilla, cream, eggs and peanut butter in North American cuisine, while East Asian cuisine makes frequent use of beef, ginger, pork, cayenne, chicken and onion.

They also identified a handful of 'authentic' ingredients that instantly bind a flavor to a cuisine – soy sauce, sesame oil, rice and ginger instantly skew a dish Asian. Paprika, onion and lard would, on the other hand, be a signature of Hungarian food.

Although food scientists do not cite health benefits as the primary driver of cuisine evolution, rather emphasizing the importance of history, economics, climate and regional habits, Ahnert said the flavor network approach could be used to predict novel flavor combinations to create a wider, more attractive variety of health options.

Food and medicine already intersect in some cuisines.

"Many flavor ingredients [such as curcumin in turmeric or ginseng] have antioxidant properties or a bioactive component," said Dr. Liu Sho Quan, of the Food Science and Technology Programme and the department of chemistry at the National University of Singapore, though large randomized trials investigating their effects are rare.

A central component of traditional Chinese medicine (TCM) is the use of "heating" and "cooling" foods to balance the body's energy that together may have a synergistic effect for health, Liu added.

Dr. Christopher Loss, director of the department of menu research and development at the Culinary Institute of America in Hyde Park, New York, US, said Ahnert and colleagues' approach could be used in reverse by beginning with ingredient combinations known to be healthful and mining the flavor network to find combinations that make them taste better.

"It does not provide a 'formula' per se, but can help catalyze the ideation process at the front end of research and development," he said. "Developing positive hedonic flavor quality is the forte of the chef"

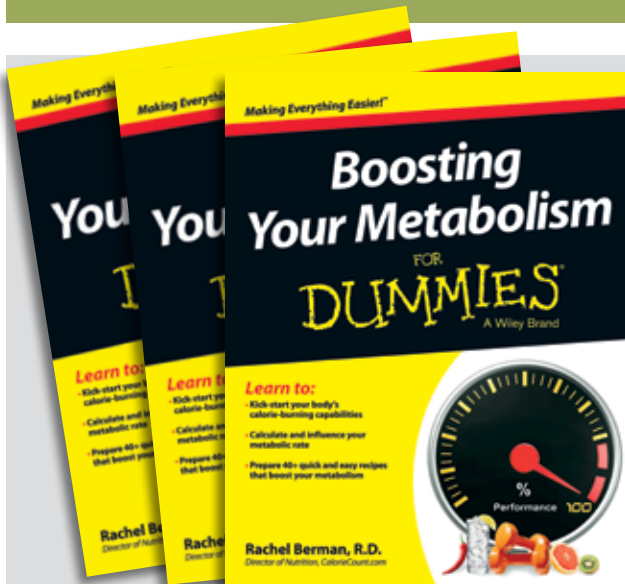
Dr. Michael Nestrud, a food scientist and director of Client Insights and Sensory Science at the culinary consultancy In4mation Insights in Boston, Massachusetts, suggested that food networks could be used to create combinations with specific functions, such as "weight loss" or "sugar free/diabetic."

Food combinations could also be modelled to fit a nutritional profile. An elderly person may need a diet that focuses on soluble fiber, calories, B vitamins, omega-3 fatty acids, iron and phytosterols.

Incorporating human behavior when building the flavor network can help identify the foods consumers will like that also fulfil the desired nutritional profile.

"These network approaches, for the first time are able to attempt to explain extremely complex patterns in how people consume food that previously we were unable to model because we didn't know how," Nestrud said.

PT



Metabolism for dummies

Rachel Berman, RD

Wiley, 2013

314 pages

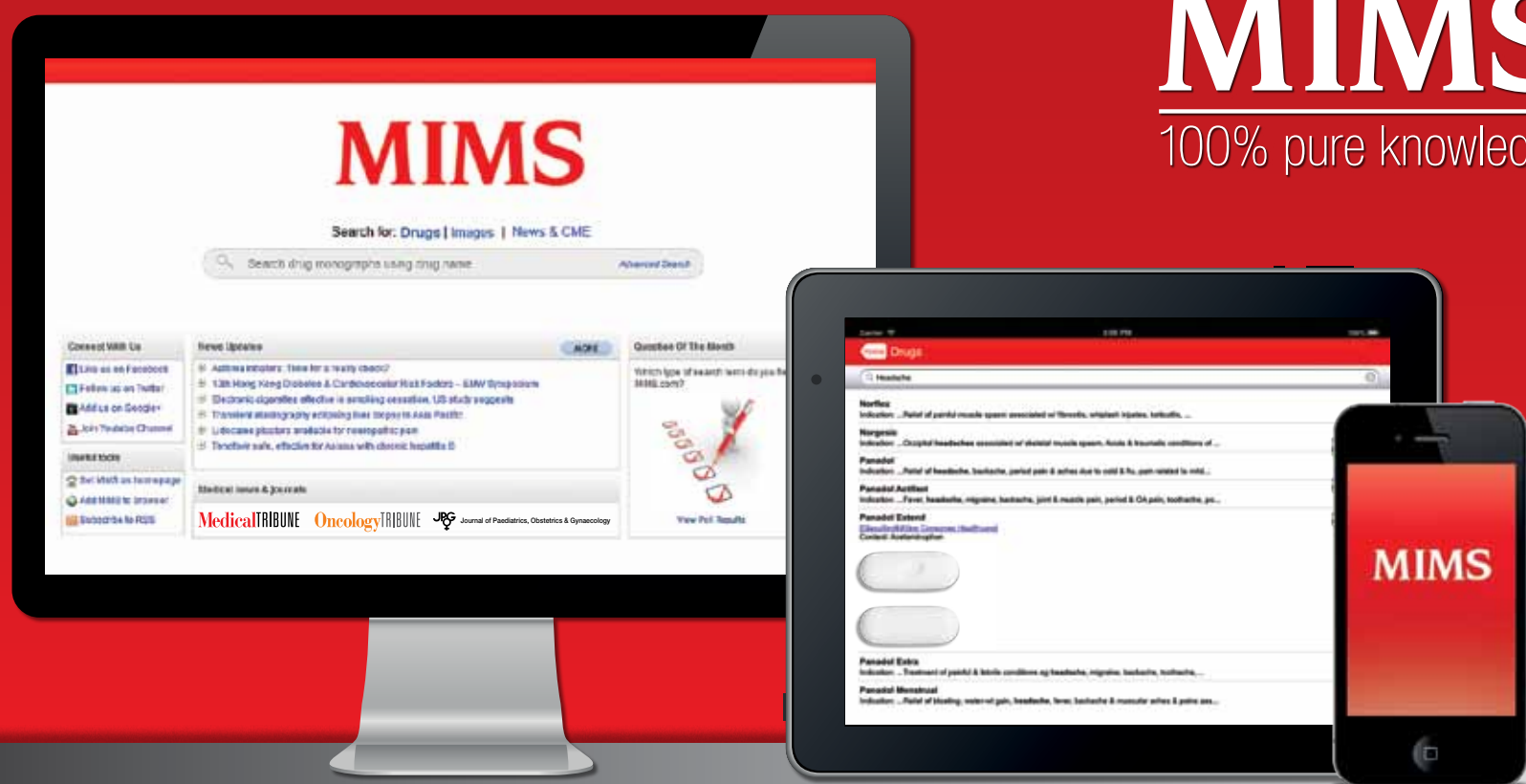
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Ever wonder why all sorts of dieting and exercise efforts sometimes result in little or no weight loss? Some of us have to work hard to simply maintain our current weight. Quite often, "slow metabolism," is blamed for these weight woes, but metabolism is much more than a means for weight loss or gain.

In *Boosting Your Metabolism For Dummies*®, registered dietitian Rachel Berman helps identify why our efforts may have failed in the past and determine how to shift one's unique metabolism into high gear by eating specific foods and performing particular exercises.

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