HONG KONG PHARMACEUTICAL JOURNAL

VOL 18 NO 2 Apr - Jun 2011 ISSN 1727-2874

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

Good Manufacturing Practice- Be prepared for Product Recall

On 23 May 2011, the Food and Drug Administration (FDA) in Taiwan announced that a plasticiser di (2-ethylhexyl phthalate(DEHP) was found to have been abused in 16 drinks. Subsequently, more foods were found to contain DEHP as well as other plasticisers, including DINP and DBP.[1] The cause of the contamination stems from the illicit use of clouding agents containing the incriminated plasticisers. These clouding agents were formulated by 2 manufacturers using the plasticisers to reduce cost and increase stability. The Taiwan FDA considered that the clouding agents might have been used in 5 major food types, namely sports drinks, juice drinks, tea beverages, fruit jam/ syrup and fruit jelly and powder and tablet supplement. The Taiwan FDA formally announced "Principle to manage the foods contaminated with plasticizers" on May 28 for the purpose of recovering the market order as soon as possible. It requested all the manufacturers and vendors of the 5 major food categories to be self-controlled and provide safety evidences for the food products on the shelves. For those that can not comply with the request, they are not allowed to sell.

Plasticisers are commonly used in certain types of plastic products, including food packing materials, blood storage bags and intravenous delivery systems to produce flexibility. Food may contain low levels of these plasticisers due to migration from the packaging materials but they should not be added to food in any quantity. The acute oral toxicities of DEHP, DINP and DBP are low. Long term exposure to DEHP is found to affect the liver and kidney as well as the reproduction and development of experimental animals. DEHP is classified as possibly carcinogenic to humans. In comparison, DINP has lower toxicity. Chronic large dose exposure to DBP was found to affect the reproduction and development and cause birth defect in experimental animals. On 29 July 2011, the Taiwan FDA announced that under the cross-departmental cooperation among the health department and all the related organizations, all of the foods with contaminated plasticisers have been removed from the shelves. Most of the removed products have been destroyed completely except those temporarily detained for judicial process of investigations. It appeared that the plasticisers contaminations are now under control.[2]

In Hong Kong, the Centre for Food Safety has maintained contact with the Taiwan FDA and promptly alerted the trade and implemented sales checks for local availability when any affected products were found to have entered Hong Kong. The HK DH also alerted the trade to check on possible contaminations of the raw materials used in manufacturing of the drugs. As a result, 5 registered pharmaceutical products imported from Taiwan and 5 other products manufactured locally as well as the Augmentin powder for syrup (156mg/5ml, 457mg/5ml) manufactured by Glaxo SmithKline Limited in France and the 375mg, 625mg and 1 g tablets manufactured by Glaxo SmithKline Limited in UK were also recalled from the market.[3] From time to time, it may be necessary for food products and pharmaceutical products to be recalled from the market. The reason could be due to wrong labeling, failure of the product to meet the specifications and/or contamination of the products. It is therefore imperative that the manufacturers, importers, distributors have a recall procedure such that in the event of a recall, the operations are effectively and efficiently carried out. The Pharmaceutical Service of Hong Kong Department of Health has issued a new recall guideline in May 2011 to assist the trade to formulate its own recall procedure. The guidelines can be found in the website: www.psdh.gov.hk.

According to GSK's in-house search, the source of the plasticisers was possibly abrasion of the polyvinyl chloride (PVC) plastic tubing used to transfer powder and granules during tablet production in the manufacturing plant in the UK. In view of this reported quality defect, the DH ordered extension of the recall to cover all Augmentin tablet formulations manufactured in UK. This report shows the importance of preventive maintenance of equipment used in manufacturing of food and pharmaceutical products. Pharmacists working in the manufacturing sector may have to take a good look at the preventive maintenance plan in their factory.

Negotiation is an ongoing process in our daily lives. Donald Chong and Alan Ng wrote on page 50 to 55 about the importance of negotiation for pharmacists in their daily practice and its impact to patient treatment outcomes. They share their insight on various principles and techniques to perform better in a negotiation.[4]

Peng Xiaofang and Cheung Hon-Yeung wrote about the functions of Docosahexanoic Acid (DHA) in Biological Membrane on page 56 to 60. DHA is an essential factor in retina and brain development, especially for infants and children. Numerous epidemiological and interventional trials have also demonstrated preventive effects of DHA on cardiovascular diseases and Alzheimer's disease. In addition, DHA is found to exert antidiabetes and anticancer effects. The article also discuss about the source of DHA from fish oil and microalgae oil. Considering the safety and substainability issues towards fish oil, more attention has shifted to the more expensive microalgae oil.[5]

Lai, Oi-Lun Ellen gave an overall view on Urinary Tract Infection and the drugs used for treatment from page 61 to 67. With the view of encouraging more pharmacy students to attend international conferences so as to broaden their outlook, the Pharmaceutical Society of Hong Kong sponsored some pharmacy students from CUHK and HKU to attend the Forbidden City Conference in Beijing from 27 to 31 May 2011. The students reported their experience on attending the Forbidden City Conference on page 83 to 86. It is encouraging to know that the Society of Hospital Pharmacist has expanded the health promotion and drug talk to the public by using a movable van sponsored by Merck Sharpe & Dohme as reported on page 87.

Baibado & Cheung reported on page 70 to 81 the neuropsychiatric properties of the root extract of Valerian. Valerian extract is traditionally used to relieve muscles spasms, to treat insomnia, hysteria, nervous tension, fatigue and menstrual cramps. Chemical analysis and clinical experiments confirm the sedative compounds present mainly in the alcoholic extracts made from the fresh roots of Valeriana officinalis. Scientific studies on the effects of the active chemical components reveal that moderate doses of valerenic acid, valepotriates and other flavonoids derived from the valerian root promote relaxation of the Central Nervous System (CNS) to reduce over active behaviours that include occasional nervousness, nervous tension, anxiety and panic attacks.[6]

References

1. www.cfs.gov.hk (Food Safety Focus, 20 June, 59th issue)
2. www.fda.gov.tw/news.
3. www.psdh.gov.hk (News Bulletin)
4. Chong, WK Donald; Ng, WP Alan (2011). The art of fine-tuning communication-negotiating skills for pharmacists.
5. Peng, Xiaofang; Cheung, Hon-Yeung (2011). Functions of Docosahexanoic Acid (DHA) in Biological Membrane and its Progress of Applications.
6. Baibado, Joewel Tarra; Cheung, Hon-Yeung (2011). Mini-Review on Neuropsychiatric Properties of the Root Extract of Valerian (Valeriana Officinalis L.).

Cheng Mary Catherine
Managing Editor
8 August 2011

HONG KONG PHARMACEUTICAL JOURNAL

VOL 18 NO 2 Apr - Jun 2011 ISSN 1727-2874

All communications and enquiries should be directed to:
The Secretary, Hong Kong Pharmaceutical Journal,
G.P.O. Box 3274, General Post Office, Hong Kong

For all enquiries regarding advertisement, please contact:
Ms Gloria Yung (Tel. 9552 2458) at the following email address:
hkpjadv@gmail.com

INSTRUCTIONS FOR AUTHORS

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

- Pharmacy Education & Practice
- Drug & Therapeutics
- OTC & Health
- Pharmaceutical Technique & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
- New Products

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

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

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

e-mail: ***editor@hkpj.org***

address: ***G.P.O. Box No. 3274, General Post Office, Hong Kong***

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

Alert on Use of Quinine Sulphate Products for Nocturnal Leg Cramps

Date: April 6, 2011

The Department of Health (DH) today (April 6) advised healthcare professionals and the public not to use pharmaceutical products containing quinine sulphate for the management of leg cramps because of possible serious and sometimes fatal adverse reactions.

Source: www.chp.gov.hk

Concerted Efforts to Combat Antimicrobial Resistance

Date: April 7, 2011

The Department of Health (DH) called on healthcare professionals and the general public to work together on the safe use of antibiotics to combat drug resistance. The call echoed World Health Organisation (WHO)'s initiative to combat antimicrobial resistance, which is the theme of World Health Day (WHD) this year. Addressing a ceremony to celebrate WHD, the Secretary for Food and Health, Dr York Chow, said that our work has been implemented with regard to the local context, while adopting multi-modal implementation strategies as advocated by WHO. The four main strategic directions adopted in Hong Kong in combating antibiotic resistance are Surveillance, Careful use of antibiotics, Infection control and Community Engagement.

Source: www.chp.gov.hk

Recall of Mercury-tainted Proprietary Chinese Medicine

Date: May 7, 2011

The wholesaler of a proprietary Chinese medicine (pCm) was ordered by Department of Health to recall 41 boxes of [Hua Tuo Brand] Youzhi Baoying Dan (Registration no.: HKP-10296) as it has been found to contain excessive mercury. The action is called for after a surveillance sample from the above batch obtained by DH inspectors from the market is found by the Government Laboratory to contain about two times the permitted limit of mercury. The drug is known to be used in children for the treatment of generalised discomfort like restlessness at night or fever.

Source: Ming Pao

Recall of Pharmaceutical Products Related to the Di-(2-ethylhexyl) Phthalate (DEHP) Incident

Date: June 1, 2011

A registered pharmaceutical product imported from Taiwan and five pharmaceutical products manufactured locally were ordered to withdraw from the market after the accident of Di (2-ethylhexyl) phthalate (DEHP) found in many pharmaceutical and food products in Taiwan.

Source: www.chp.gov.hk

The Prevention and Control of Disease Ordinance (Cap. 599) Has Been Amended after the Outbreak of A Hemolytic Strain of Escherichia coli in Germany

Date: June 10, 2011

In view of the outbreak of a deadly *E. coli* which cost 18 lives in German, the Hong Kong Government has amended the Prevention and Control of Disease Ordinance (Cap. 599) to include Shiga toxin-producing *Escherichia coli* (STEC) infection as one of the statutory notifiable diseases. The new requirement on notification will cover not only the existing *E. coli* O157:H7 strain, the most common strain detected in Hong Kong, but also *E. coli* O104:H4 on cases of STEC infection.

Source: http://www.chp.gov.hk/ceno.

Suspected Poisoning due to Tropane Alkaloids Tainted Chinese Medicinal Herb

Date: June 18, 2011

Clinic records showed that some 150 clients were probably prescribed with a contaminated Chinese medicinal herb Rhizoma Atractylodis since May 23. A spokesman from DH explained that the finding was made after the Department investigates into a notification from the Hospital Authority of a suspected case of Chinese herbal medicine poisoning. The patient was a 50-year-old woman who had taken a self-prepared herbal decoction, with the herbs obtained from the above CMP for easing of her perimenopausal symptoms. Analysis by the Government Laboratory on samples of Rhizoma Atractylodis obtained from the clinic confirmed contamination by tropane alkaloids.

Source: www.chp.gov.hk

Scientific Committee's Recommendations on Influenza Vaccination for 2011/12 Season

Date: June 21, 2011

Given serious influenza infection can occur even in healthy individuals and influenza vaccines are safe and effective, a Scientific Committee on Vaccine Preventable Diseases (SC) under the Centre for Health Protection (CHP) of the DH has made updated recommendations on the use of seasonal influenza vaccine for the coming influenza season (2011/12). The recommendations are made based on updated scientific observations in the 2010/11 winter influenza season. Nine priority target groups have been recommended by the Committee for seasonal influenza vaccination in the 2011/12 season. The Government Vaccination Programme (GVP) and Vaccination Subsidy Scheme (VSS) 2011/12 will continue to provide free and subsidized vaccination respectively to the same target groups as last year.

Source: www.chp.gov.hk

Action Plan to Promote Healthy Diet and Physical Activity Participation in Hong Kong

Date: June 22, 2011

In response to a call made in the Government's strategic framework document *"Promoting Health in Hong Kong: A Strategic Framework for Prevention and Control of Non-communicable Diseases"* published in 2008, a Working Group on Diet and Physical Activity has disclosed their study and made suggestions for Hong Kong citizens to adopt healthy lifestyle habits as early as possible so that the risk of contracting non-communicable diseases during adulthood and beyond could be lowered.

Source: www.chp.gov.hk

Woman Arrested for Allegedly Selling Slimming Products with Undeclared and Banned Drug Ingredients

Date: June 24, 2011

An 18-year-old woman was today (June 24) arrested in a joint operation by the Police and the Department of Health (DH) as part of their follow-up investigation into the sale of 2 slimming products, "8 Slimming Effects – All in One（青春少女型）" and "8 Slimming Effects – All in One（貴夫人型）", which were earlier found to contain undeclared and banned drug ingredients that may cause serious side effects.

Source: www.chp.gov.hk

The Art of Fine-tuning Communication – Negotiation Skills for Pharmacists

CHONG, WK Donald*; NG, WP Alan
Pfizer Corporation Hong Kong Limited, 16/F, Stanhope House, 736 King's Rd, North Point, Hong Kong SAR, China
(Corresponding author)*

ABSTRACT

Negotiation is an everyday practice for every individual, and pharmacists are of no exception. This article will focus on discussing the ways and skills to improve communication in negotiation. The article also aims at innovative ideas to enhance communication, and discuss on the significance of negotiation to pharmacy practice and its impact to patient treatment outcomes.

Keywords: *negotiation, communication, pharmacist skills, continuing education.*

INTRODUCTION

To solve a dispute, we may choose different approaches. One may choose to avoid, to confront or to solve by multiple tries. These methods of resolution generally cannot provide the best solution for the dispute, instead, we may negotiate. Negotiation plays an important role in our daily lives, whether it is for business or personal situations. It is a dynamic process whereby two or more parties seek an agreement to establish what each shall give or take, to perform or receive in dealing with the transaction. The purpose of negotiation is to establish a point where convergent and divergent interests are kept for the involved parties.[1]

As pharmacists, negotiation occurs with patients on drug therapies and suggestions; with doctors on therapeutic drug choices and business negotiations are our everyday jobs. The success of negotiation is often not a matter of chance, but the result of good planning and specialized skills. Negotiation skills can sometimes be inborn, but mostly it has to be learned. Equipping ourselves with these skills can help to optimize working efficiency and help to best allocate resources.

In this article, we will first explore the definition of negotiation. Then we will look into details about the elements affecting negotiation. By understanding the counterpart, one can then choose suitable languages of negotiation. The article will also focus on different negotiation strategies. Finally, there will be a discussion on the importance of win-win outcome, which is the reason why we negotiate.

WHAT IS NEGOTIATION?

Negotiation is a process of 'bargaining' on a common issue, which means that the negotiation process is a diametrical competition between the involved parties. Negotiation is divided into two types: positional negotiation and principle negotiation. Positional negotiation refers to the fact that each party begins with an extreme position for own interests with little regard to the other party; generally the involved parties will not come to an agreement. While principle negotiation focuses on interest, which means the involved parties bargain to seek for mutually beneficial solutions to a shared problem. Principle negotiation is the focus of this article and will be discussed here.

'Principle negotiation' may be further divided into two types: 'distribution bargaining' and 'integrated bargaining'.[1] 'Distribution bargaining' is a fixed-sum negotiation where the involved parties share a fixed quantity of the 'negotiation pie'; the pie may be divided equally or it may not. 'Integrated bargaining', on the other hand, is where both parties may win or lose on some points, and the size of 'pie' may change during the negotiation process. Some people would like to describe the resulting parties as a 'loser' or a 'winner'. However, in principle negotiation, these terms are relative and the 'winner' simply means the one who get closer to his or her initial objectives.

Since different individuals have their own characters and styles, negotiation can be a cross-cultural activity. Individuals have personality differences in terms of communication style and experience, organizational backgrounds, family backgrounds or any other factors that may influence communication and conflict management. These personal inclinations can affect negotiation, which may eventually affect the final result of negotiation.

ELEMENTS AFFECTING NEGOTIATION

Negotiation can start as soon as one select an issue and start selling or dealing with the opposing party. Before one actually gets started with the negotiation, it is suggested to estimate and validate the negotiation goal and plan for what agreements or disagreements may be best acceptable. There are different models describing the elements affecting negotiation, one of these systems is described by the acronym ICON, which includes four basic components: [2]

1. **Interests** – the subjective needs, concerns and desires of the involved parties;
2. **Criteria** – objective standards to filter and judge which option is the best;
3. **Options** – are the possible solutions which shared or conflicting interests are satisfied;
4. **No-Agreement** – what the parties will do if they cannot come to any agreement.

These four basic elements are the essential considerations before negotiation actually starts. Without these elements, the negotiation cannot have a solid foundation to proceed.

Additionally, in order to have a smooth negotiation process, other variables need to be determined. Three key factors of negotiation will be

discussed, namely 'value', 'power' and 'time'.

Value

It is believed that thinking simultaneously on creating value and claiming one's interest is critical to achieve any win-win results. This affects how both sides behave and in turn affects results of negotiation. Those overestimate the value of their offers may behave in a way that makes impasse more likely. On the other hand, those who underestimate the value of their offer tend to move too quickly and give up value to the other side. Therefore, understanding our offer and the corresponding outcome is critical in making a fair negotiation.[3]

Here is a practical example. Assume a hospital pharmacist wants to find out whether dispensing errors can be minimized by hiring more staffs to reduce the workload of other colleagues. He/she may request to increase the manpower in the pharmacy. The decision maker may have different considerations to determine the 'value' of hiring new staff:

- How much will it cost to increase the manpower?
- How will the service quality be affected?
- To what extent will the dispensing accuracy be improved?
- Will this be beneficial on a long-term or a short-term basis?

Therefore, we can see that every individual has different considerations and priorities that can affect the bargaining result. We should strive for a balance in terms of different 'values'. Since every negotiator has his upper and lower limits for interests gained rather than a fixed sum, a zone of offering that may result in an agreement should be determined. It ensures more flexibility and can maximize the benefits gained.

Power

'Power' is referred to the ability to influence people or situation. Power can come from multiple sources of values and characteristics including:[1],[3]

1. **Position** – the formal position of the negotiator in an organization, a higher position indicates more influences to decision making;
2. **Knowledge** – negotiators with more information and knowledge can more likely affect the result of negotiation;
3. **Relationship** – the scope of cooperation depends on personal relationship; the more trustworthy individuals hold more power;
4. **Rewards** and punishment – the one with greater ability to reward or punish holds more power;
5. **Lack of interest** – the side less interested in what is being negotiated holds more power, which implies that one should not let others know how important the negotiation means to the person;
6. **Gender** – dealing with opposite sex can confer power;
7. **Personal power** – refers to passion and confidence. Higher self-esteem also makes one feel to have various options when the negotiation fails.

Using the above example in hiring a new staff for pharmacy, we know that the department manager of the pharmacy holds more power in decision making. Since the decision maker holds a higher position and may lack interest in this topic, he/she can end the negotiation using his absolute power. On the other hand, if the pharmacist has much personal power and good relationship with his/her boss, then he/she may be able to convince the boss with his knowledge and arguments.

Power can be real or apparent, which means that when one is able to make the other believe he/she has more power, then consequently, he/she has more influences on the final result. How much power one actually acquires can only be confirmed by testing the reality; therefore we should not underestimate our influence.

Time

Pareto's Principle proposes the 80/20 rule, which means that 20% of what one do can produce 80% of the results.[6] Adopting this principle, Slark suggests that 80% of the results gained from negotiation may be agreed in the last 20% of the time of negotiation.[5] Therefore, understanding that time and deadlines can favor either side; we need to know how to avoid making unwise decisions when the time is running short. Here are some tips:

1. **Be patient** – remain levelheaded and wait for the best moment to act;
2. **Be persistent** – try different strategies for own stand-points instead of giving up;
3. **Realize deadlines can be changed** – do not panic when deadline approaches. Realize deadline may be changed to achieve the best outcome;
4. **Know the counterpart's timeline** – know counterpart's timeline and hide up own one. As the counterpart's deadline approaches, he/she may feel more pressure and hence more likely to make concessions.

Elements that can influence a negotiation can vary in different cases. As illustrated above, 'interest', 'value', 'power' and 'time' form the basis of negotiation. By understanding these influencing factors, we can better prepare ourselves.

UNDERSTANDING YOUR COUNTERPARTS

Negotiation is important especially when there is no structure to rely on for resolving a problem. It is not concerned with trying to reach a compromise but to obtain the best possible result for parties involved. Before this can be achieved, a good understanding of your counterpart can make communication more effective.[7]

Maslow's Hierarchy of Needs

Everyone has needs, starting with basic elements essential to life to more spiritual satisfaction. A successful negotiation will not only require satisfying the desires but also the ability to make the negotiators feel comfortable and respected. Maslow has classified all human needs into five categories well-known as the 'Hierarchy of Needs'. As illustrated in Figure 1, the two negotiators have different extent of needs at each level. Therefore, the offerings to each counterpart need to be tailor-made.[1],[8]

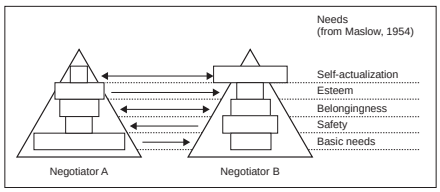


Figure 1. *Maslow's Hierarchy of Needs illustrates different desires in negotiation.*

People's needs may change from time to time. As an example, in a pharmaceutical company, the boss may recognize the performance of an employee in different ways. At first, the employee may be rewarded with increased salary. To further recognize his effort, he/she may be promoted; gradually the person will build up a sense of belonging to the company and increase self-esteem. When time goes on, the employee may already be satisfied with his salary and position, then 'self-actualization' will play an important role. By fulfilling the psychological desires like self-recognition and satisfaction, the employee may be self-motivated to do even better. This happens to all negotiation parties as well.

Therefore in negotiation, the parties involved should offer a combination of

needs. Once the needs of negotiating parties have been recognized, they will become part of the 'negotiating pie'. This implies that both parties must be able to offer sufficient objectives or concessions that are valuable to the other. Consequently a careful planning of offerings should be worked out before a negotiation actually happens.

Understanding the situation of patients

In providing health care services, dealing with difficult patients can be the most challenging job pharmacists need to do on a daily basis. Patients may come with irritations and frustrations due to their medical conditions or other sufferings. These patients may not know what to expect, and what medical services they can get. The lack of power may make the patient feel uncomfortable and they may want to regain some control by releasing their frustration on their health-care providers.[9]

As an example, a community pharmacist encounters many different patients within one single day. However, all of these patients come with a common desire – to obtain help and counseling. Those difficult patients also expect the pharmacists to show empathy and respect them. Due to the fact that not all patients are willing to strictly follow all recommendations from pharmacists, the communication process probably involves negotiations to find suitable solutions and concessions on the therapy chosen, compliance problems and non-pharmacological interventions. Negotiation can thus ensure optimized individual patient care.

We can see that patients want a 'package' of offerings, in addition to basic needs of medications and counseling services, they also want spiritual satisfaction. Therefore, interpersonal skills and negotiation skills are critical for dealing with patients. In particular, it is important to act in accordance with client's wishes. An expression of understanding of patients' feelings will be helpful in these negotiations.

Neuro-Linguistic Programming

An emerging idea to understand the opponent can be derived from Neuro-Linguistic Programming (NLP), which was started in the 1970s. NLP states that a person is a whole mind-body system with consistent and patterned connection between neurological processes, language used and behaviors for expression. Implementation of NLP in negotiation may make one more easily understand and get into the mind set of counterparts. It is suggested that communication between two people using two different representational systems is difficult and can easily result in irritation. Therefore, a system named as 'Preferred Representational System' (PRS) mentioned in the NLP aims to make communication more effective and harmonized.[10-12]

The PRS model suggests that people access their thoughts differently and this difference corresponds to three principal senses: seeing, hearing and feeling. People have an unconscious preferred way of dealing with the world; therefore all people can be categorized into three types: visual, auditory or kinaesthetic. PRS manifests itself through choices of wordings when communicating and eye movements when thinking.

By listening to people's speech, it is also possible to identify their PRS. For example, the visual persons prefer to use wordings like 'I see how', 'It looks like'. On the other hand, auditory persons like wordings such as 'It sounds that', 'I hear how' or 'In harmony'. Conversely, kinaesthetic persons may say 'It feels like', 'I can grasp' or 'Get in touch'. People typically favour one sensory modality over the others. By listening to their words, one can switch the language to be the same as counterparts'. This creates a harmonized environment, allowing cooperative agreement to be more easily achieved.

NLP also states eye movement can reveal meaningful cognitive patterns. A person's favoured representational system can be identified by the most frequent type of eye scanning while the person is thinking. As shown in Figure 2, visual persons have an unfocused or upward movement of eyes; auditory persons have eye movements in the midline; while kinaesthetic persons often have eye movements below the midline.[13, 14]

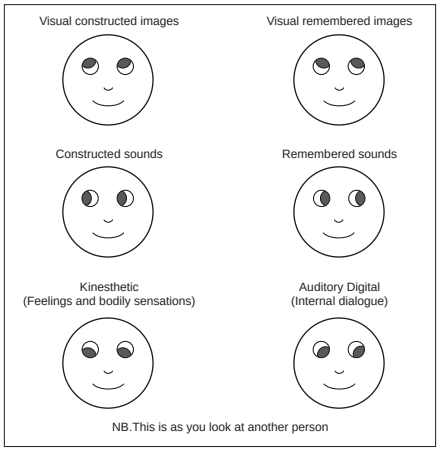


Figure 2. *Eye movement cues for PRS.*

People can achieve close relationship with visual persons by mirroring the client's behaviour. They will find the counterpart look familiar and friendly. Auditory individuals prefer words or sounds for communication, while kinaesthetic persons prefer messages that reflect feelings or physical actions. NLP suggests possible hints for better communication which makes negotiation more effective and cooperative.[15]

The understanding and in-line communication style is important for friendly negotiation. NLP is a possible tool to help negotiators achieve a good relationship. All the skills mentioned suggest a common goal for a better understanding of our counterparts. However, the methods used for communication in negotiation can also be challenging. In the coming section, skills used for verbal communications will be explored.

LANGUAGE OF NEGOTIATION

A good negotiator is usually a good communicator. He/she is able to grasp and process information rapidly and effectively. Every individual has his own negotiation style, for example, to be competitive or cooperative, to make accommodation or to avoid. These personal inclinations may support certain strategic positions better than the others. A good negotiator should be able to change his communication style to play every part of negotiation competently. Similar to the idea of NLP, if personal preferences can be overcome, the effectiveness of negotiation can be enhanced. This idea is illustrated in Figure 3.[1]

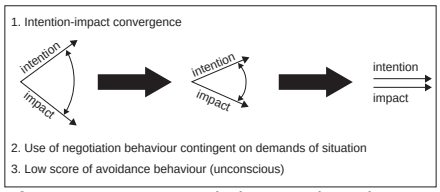


Figure 3. *Negotiation style changes according to the challenge can maximize the impact of effort input.*

Building trust

Earning trust from our counterpart is the first step for successful cooperative negotiation. It is a series of actions that builds up one's honesty, integrity and reliability. It is a cycle and enables a long-term relationship establishment (Figure 4). To earn trust, putting effort in multiple aspects is essential:[5]

1. **Maintain a professional appearance**

– apart from clothing, also enhance the appearance with good posture, voice and nonverbal signals;
2. **Demonstrate competence** – support the points with expertise and knowledge;
3. **Keep promise** – do as what have been said to build reliability;
4. **Listen** – exercise active listening and recognize counterpart's opinions and positions;
5. **Provide accurate information** – not to hide information from counterparts in order to build a lifelong relationship based on trust;
6. **Take calculated risks** – at risk, both parties build trust rapidly.

Building trust is particularly important in negotiation between pharmacists and patients. As we have observed from the daily practice of pharmacists, they are required to maintain a professional appearance. A patient based approach involves active listening for patients' enquiries and formulation of proper response with the support of professional knowledge and judgments. Pharmacists also need to provide information on the side effects of medications, but not trying to hide this information from patients. The provision of adequate and accurate information is our daily work; it forms the basis of patients trust on our professionalism.

Building trust requires multiple skills and approaches. In particular to communication, 'listening' is one of the key determinants for a successful negotiation. The ensuing sections will discuss ways to improve our listening skills for better communication.

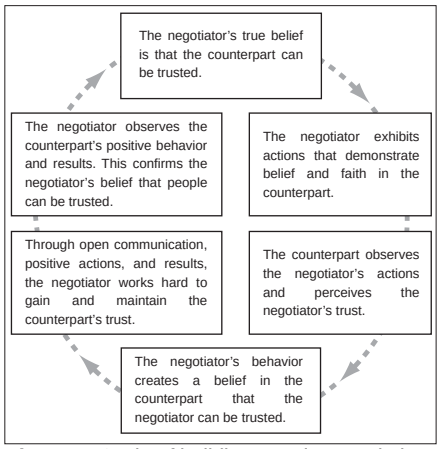


Figure 4. *Cycle of building trust in negotiation.*

Listening

To create a win-win situation, it is necessary to understand our counterparts' needs, wants and goals. 'Active listening' is the key for gathering all the essential information. In addition, it is important to pay attention to their actions, reactions, and gestures. All these give us clues to our counterparts' thoughts. We should pay attention to all signals and listen attentively:[5]

1. **Be motivated to listen** – the amount and type of information one wanted;
2. **Let the counterpart tell his/her story first** – this enables one to tailor the presentation according to needs stated;
3. **Not to interrupt** – it may disturb the potential useful information coming up
4. **Fight off distractions** – avoid interruptions and distractions;
5. **Write things down** – conflicting information may come up with separated presentations, pointing out the error can earn power;
6. **Eye contact** – this perceived as trustworthy and honest;
7. **Not to get angry** – emotions can hinder one's ability to listen or think effectively;
8. **Listen and speak** – respond so that the counterpart can react.

To listen and react appropriately; one needs to ensure there is correct understanding of messages delivered. The skills include clarifying, verifying and reflecting. Clarifying and verifying ensures that one gets the details and truly understands the messages delivered. Reflecting means making remarks and showing empathy for the speaker's feeling. Before all, responding needs full understanding of messages behinds the contents; also to point out emotional or unexpressed meanings. Interactive listening allows gaining more explanation and information, which can aid one to obtain the required data from opponent side.

Listening is the critical key to obtain information and helps in setting strategies for negotiation. Pharmacists are the safeguards of patients' health. Without listening skills, we will not be able to satisfy patients by fulfilling their desires. Therefore, to become a good pharmacist negotiator, we should equip ourselves with these essential skills. In addition, the implementation of 'active listening' also involves skillful questioning. The techniques will be mentioned in the next section.

Questioning skills

Questioning enables negotiators to obtain the maximum amount of information possible to develop negotiation strategies. It is challenging to ask meaningful and useful questions. Generally speaking, there are two types of questions: closed-ended and open-ended.[5]

Closed-ended questions usually help in seeking for a specific piece of information, in which the answer is either 'yes' or 'no'. These types of questions are not limited to obtain simple and direct information, but also useful to direct a conversation. For example, in patient education, you may ask: 'you will take the medicine accordingly, right?', this will force your patient to promise you on compliance of medication and the counseling can move on to discuss side effects of medications. Secondly, closed-ended questions can break the ice and get a conversation started, it is typical to start the conversation by asking: 'are you feeling better today?'. Thirdly, these questions are helpful when trying to gain a point from your opponent or make clarifications. For example, to encourage patients to have regular blood glucose monitoring, you may ask: 'can you promise to regularly check your blood glucose if a pack of free sample test paper is provided?' These illustrate that close-ended questions can help gain a concession from your counterpart.

The open-ended questions often enable one to obtain more information than the closed-ended questions. They usually begin with who, what, where, when, how or why. For example, you may ask: 'why you are not taking the drugs according to instructions?' in order to identify the possible hurdles for patient compliance. And we may occasionally ask: 'How do you feel after taking the medication?' in checking for both efficacy and safety of medications. Other than gaining information like objectives, needs or desires, these questions are effective when you want to uncover your counterpart's behavioral style and mind-set.

In general, questioning can be useful in many facets, in particular to gain or give information, to guide the negotiation, to reach agreement by testing the distance between negotiators' goals or to reduce tension in negotiation. Therefore, questioning is an important skill to shift negotiation forward.

Non-verbal communication

It is suggested that non-verbal behaviours play the most important part in face-to-face communication. Learning non-verbal communication is difficult yet important. It is possible to interpret the inner thoughts by looking at facial expressions; in particular, the eyes can open the window into our soul. Here are some possible meanings of the corresponding expressions:

1. **Broken eye contact** – try to hide something;
2. **Unfocused eye contact** – gaze past or glance around means getting bored;
3. **Piercing eye contact** – angry emotion;
4. **Steady eye contact** – generally reflects that a person is honest and trustworthy;
5. **Head turned slightly** – evaluating what one is saying;
6. **Tilted head** – may indicate the listener is uncertain about what is being said;
7. **Smiling** – confident or in agreement with the speaker.

Changes in body, arms, hands and leg gestures can also indicate different feelings like nervousness, confidence, getting bored or some other possible emotions. These are shown in Table 1 for linking personal thoughts and behavioral changes.[5]

Gaining understanding from non-verbal signals enables pharmacists to observe and respond to expressions of patients or doctors. We should be aware and we shall pay attention to these clues; this is difficult yet this can make a negotiation more effective.

Overall, we know that language used for negotiation can be an important determinant for the success of negotiation. Building trust is the first and most important step for friendly cooperation. Suitable implementation of listening skills, questioning skills or even body language can help in negotiation. From all these, we can see that skillful negotiations need to be supported by various communication techniques.

Table 1. The language of nonverbal communication.

Dominance and Power	**Submission and Nervousness**
Placing feet on desk Making piercing eye contact Putting hands behind head or neck Placing hands on hips Giving a palm-down handshake Standing while counterpart is seated Steepling (fingertips touching)	Fidgeting Making minimum eye contact Touching hands to face, hair, etc. Using briefcase to "guard" body Giving a palm-up handshake Clearing throat
Disagreement, Anger, and Skepticism	**Boredom and Lack of Interest**
Getting red in the face Pointing a finger Squinting Frowning Turning body away Crossing arms or legs	Failing to make eye contact Playing with objects on desk Staring blankly Drumming on table Picking at clothes Looking at watch, door, etc.
Uncertainty and Indecision	**Suspicion and Dishonesty**
Cleaning glasses Looking puzzled Putting fingers to mouth Biting lip Pacing back and forth Tilting head	Touching nose while speaking Covering mouth Avoiding eye contact Using incongruous gestures Crossing arms or legs Moving body away
Evaluation	**Confidence, Cooperation, and Honesty**
Nodding Squinting Maintaining good eye contact Tilting head slightly Stroking chin Touching index finger to lips Placing hands on chest	Leaning forward in seat Keeping arms and palms open Maintaining great eye contact Placing feet flat on floor Sitting with legs uncrossed Moving with counterpart's rhythm Smiling

NEGOTIATION STRATEGIES

After the introduction of ideas in planning and communication skills for negotiation, we need to know when to use them. According to the Conflict Mode Instrument proposed by Thomas Kilmann, there are five basic positions in a given conflict, as shown in Figure 5.[4]

1. **Competition** – to compete for interests, not cooperative;
2. **Collaboration** – an attempt to find a solution which satisfies desires and interests of all parties;
3. **Compromise** – achieve a solution that is tolerable by all parties;
4. **Avoidance** – no win solution, the negotiator withdraws from the conflict;
5. **Accommodation** – opposite of competition, very operative that even sacrifices own interest.

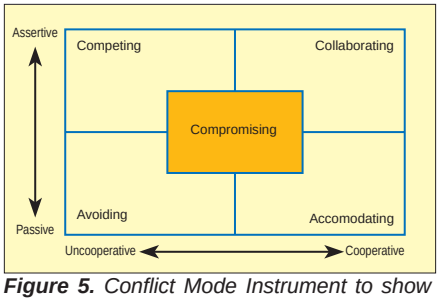


Figure 5. *Conflict Mode Instrument to show basic positions of a conflict.*

According to individual preferences, one should understand the opponents' position, say who likes to push his way through, who tends to draw back or who will be more comfortable in looking for new alternatives. Understanding the opponent side can therefore facilitate the choice of own position.

The idea of Conflict Mode Instrument can be visualized as five fundamental dance positions to demonstrate mental flow between negotiators. As shown in Figure 6, the five strategies for negotiation corresponding to the positions hold are namely 'pushing', 'pulling', 'standing still', 'disengaging' and 'engaging'. Starting from the middle position, the negotiator with more power can attempt to push or pull the other on distribution axis for a competition of common interests. The negotiators can move together along the integrative axis by using creative and cooperative approaches. These strategies intend to engage each other for a joined movement towards collaboration agreement.[1]

'Pushing' is being competitive. It involves evaluation on counterpart's suggestions and proposals. It also refers to a request or to assert pressure on the other side. The success of a 'push' is needed to be backed up with justifications or explanation. The negotiator with more power can perform 'pushing' more easily.

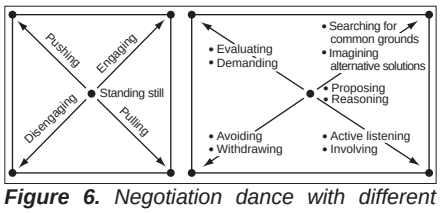


Figure 6. *Negotiation dance with different words of representation.*

'Pulling' is being accommodative and it involves responding to questions. The person being 'pulled' is drawn to the desired direction. Active listening is the key for 'pulling'. By summarizing and interpreting the message received, the negotiator may make comments and re-direct the negotiation.

The 'standing spot' refers to compromising. 'Standing' does not mean to hold position without changes, but to move on the spot with small steps. By testing and proposing new ideas, both sides are trying to find out an acceptable solution. If the best choice is the current proposal, then this position will mean making small compromises.

'Disengaging' refers to avoiding, which means moving away from negotiation. This action needs to be carefully done. Disengaging involved actions like humour to release tension, distracting or even leaving the negotiation room. These withdrawing actions allow space for thinking and can also create a break.

'Engaging' is being collaborative, the negotiating parties move together for a constructive collaboration. It is built on a basis of common goal. New ideas to satisfy expectations of both parties may be introduced. Engaging enables the achievement of mutually beneficial agreements.

As a daily example, we can look at the practice of pharmacists. Pharmacists are always trying to select the best treatment option for patients; however in actual situations, patients have variables that can affect the therapeutic choices. If a patient is having heart failure, the doctor may initiate a beta-blocker. The clinical pharmacist may have to take other parameters into considerations such as the age, heart rate and the stage of disease. Then the pharmacist may start a negotiation with the doctor using the five strategies. He may first use 'pulling' to understand the rationale of choosing beta-blocker and express his concerns. Then he can 'push' to evaluate the use of beta-blockers in that specific patient, with the back-up of justifications and evidence. The doctor may disagree, and then the pharmacist may try to 'engage' the negotiation by suggesting other drug alternatives. 'Disengaging' may be used if the negotiation falls into a deadlock;

disengaging allows space for thinking and re-directing. Finally, the negotiation may end at the 'standing spot', which means that only small compromises are made, for example having heart rate monitoring with suitable dosage adjustments.

We can see from the example that negotiation is not about holding a fixed position or strategy, but may change as the negotiation proceeds. Steps in the negotiation dance are not limited to the above positions. There may also be intermediate steps, pauses, turns and jumps. Different styles of negotiation can be influenced by personal attributes and multiple factors. Since strategies vary from time to time, a good negotiator should be able to use different approaches and techniques in dealing with parties involved.

NEGOTIATION OUTCOMES

There are basically four types of outcomes for negotiation, namely win-win, win-lose, lose-lose and no agreement. The result can be affected by the difference in valuation, which allows exchange of features that one is less interested in for other features that are more attractive. However, if both negotiating parties have exactly the same valuation, they probably will not voluntarily compromise. The negotiation may finally end up by sacrificing either side. By winning and losing different positions, an agreement can be settled. Figure 7 shows the distribution of points that two negotiation parties shares, the variations in gains means different outcomes.[1],[5]

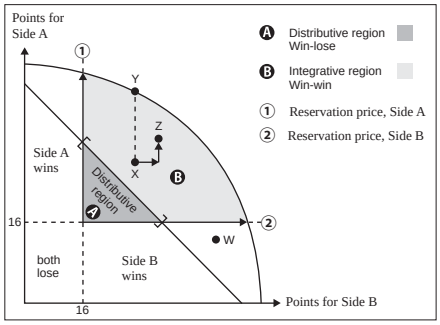


Figure 7. *Relationship between four different outcomes with variation in achievements*

'Win-win' outcome is essential to build a feeling of willingness to negotiate and cooperate with each other again. This is an ideal outcome yet a usual outcome for most negotiations; both parties will be able to gain something which makes them feel satisfied.

'Win-lose' negotiations will have one counterpart wins and the other loses. The loser is likely to refuse negotiating with the winner again if there are other choices. This cooperation will finally end up in lose-lose situations in the long run.

'Lose-lose' outcomes may result when neither party achieves their needs. It is often a result when both parties insist on their own perspectives with no collaboration. The involved negotiating parties may build a poor relationship. Some people may suggest preventing this situation by convincing the counterpart to cooperate and to show him the consequences of a no-agreement deadlock.

The fourth possible result of negotiation is 'no outcome', which means neither party wins or loses. Since there is no agreement drawn, the negotiation stops with no result. Both parties may be willing to come back to the negotiating table for other issues or when there are new ideas or solutions.

Since the win-win outcome can ensure a friendly relationship, there are other suggested methods to achieve the desired outcome more easily. The key idea is to avoid narrowing the negotiation down to one issue. A typical example of narrow discussion topic is the negotiation over prices, usually the seller will lose or there will be no outcome in the end. Therefore, as mentioned in the previous section on Maslow's Hierarchy of Needs, a package of values should be offered. Negotiating parties do not have the same needs and wants; the exchange of desires and objectives is the basis for a win-win agreement.

CONCLUSION

Negotiation is an essential element of communication for every individual including pharmacists. The ultimate goal of negotiation is to find a win-win solution for a particular situation through the collaborative work of negotiating parties.

Various principles and techniques are suggesting methods on how to perform better in a negotiation. Some ideas in common are building a trusting positive relationship between negotiating parties, adequate planning and emphasizing the importance of collaboration. In addition, we should also be aware of individual variations that may account for differences in negotiating strategies and attitudes.

All of us try to strive for the best solution and treatment outcomes for patients. No matter whether you are a hospital pharmacist, a community pharmacist or an industrial pharmacist, better patient care is our common goal. Therefore, we should equip ourselves with sufficient skills to deal with the increasingly complex and comprehensive patient care. Negotiation can become one of the major communication methods in different situations, including making deals with business partners, the government, doctors or our patients. Through daily practices, negotiation skills can be polished. This is the key to become a successful negotiator.

Author's background

CHONG WK Donald *is a registered pharmacist. He is currently the Medical Affairs Manager of Pfizer Hong Kong. For more information about this article, please contact him through his email address: wing-kit.donald.chong@pfizer.com*

NG WP Alan *is a pharmacy intern working in the Medical Department of Pfizer Hong Kong. His email address is: susunhk@hotmail.com*

References

1. Saner, Raymond (2004). *Expert Negotiator*. Martinus Nijhoff Publishers.
2. Lum, Grande (2004). *Negotiation Fieldbook*. McGraw-Hill Professional Publishing.
3. Dietmeyer, Brian Bazerman, Max Kaplan, Rob (2004). *Strategic Negotiation: A Breakthrough Four-Step Process for Effective Business Negotiation*. Dearborn Trade, A Kaplan Professional Company.
4. Thomas Kilmann (1974). Conflict Mode Instrument. Accessed on February 14 2011. http://www.amazingpeople.co.uk/thomaskilmann.htm
5. Stark, Peter B. (2003). *Only Negotiating Guide You'll Ever Need: 101 Ways to Win Every Time in Any Situation.* Broadway Books.
6. Vilfredo Pareto. Pareto Principle. Accessed on February 15 2011. http://en.wikipedia.org/wiki/Pareto_principle
7. Bateman, Neil. (2000). Advocacy Skills for Health and Social Care Professionals. Jessica Kingsley Publishers.
8. Abraham Maslow (1954). Maslow's Hierarchy of Needs. Accessed on February 15 2011. http://www.edpsycinteractive.org/topics/regsys/maslow.html
9. Keith Kriet. (2008). Enhancing and Using Negotiation Skills. *Dermatology Nursing/April 2008/Vol. 20/No. 2.*
10. Aldert Vrij, Shara K.Lochun. (1997). Neuro-Linguistic Programming and the Police: Worthwhile or Not? *Journal of Polic and Criminal Psychology, Volume 12, No. 1, 25-31.*
11. A Wisdom Archive on Neuro-Linguistic Programming. Accessed on February 15 2011. http://www.experiencefestival.com/neuro-linguistic_programming
12. Paul Tosey, Jane Mathison. (2010). Neuro-Linguistic Programming as an Innovation in Education and Teaching. *Innovations in Education and Teaching International Vol. 47, No. 3, August 2010, 317-326.*
13. Joseph O'Connor, Andrea Lages. (2004). *Coaching with NLP: How to be a Master Coach.* London : Element.
14. Michael Buckner and Naomi M. Meara. (1987). Eye Movement as an Indicator of Sensory Components in Thought. *Journal of Counseling Psychology 1987, Vol. 34, No. 3, 283-287*
15. Dorothy Young Brockopp. (1983) What Is NLP? *The American Journal of Nursing Vol. 83, No. 7, pp. 1012-1014*

Functions of Docosahexanoic Acid (DHA) in Biological Membrane and Its Progress of Applications

PENG, Xiaofang; CHEUNG, Hon-Yeung
Research Group for Bioactive Products, Department of Biology & Chemistry, City University of Hong Kong SAR, China

ABSTRACT

Docosahexanoic acid (DHA, C22:6) is an important Omega-3 polyunsaturated fatty acid with favorable health benefits. DHA is a major structural component in biological membranes and known as an essential factor in retina and brain development, especially for infants and children. Numerous epidemiological and controlled interventional trials have also demonstrated preventive effects of DHA on cardiovascular diseases and Alzheimer's disease. In addition, DHA is found to exert antidiabetes and anticancer effects. This paper mainly reviews beneficial effects of DHA and introduces major sources of DHA. At last, the suggested daily intake and application progress of DHA is also summarized.

Keywords: *Docosahexanoic acid, polyunsaturated fatty acid, fish oil, plasma cholesterol, cardiovascular pathology, Alzheimer's disease, cell membrane, inflammation mediators*

INTRODUCTION

Docosahexanoic acid (DHA, C22:6 n-3) is a predominant Omega-3 polyunsaturated fatty acid (Fig. 1) found abundant in biological membranes. As a major constituent of membrane phospholipids of important neural structures, DHA specifically concentrates in human brain and retina,[1,2] which implicates essential roles of DHA involved in visual and brain development (Fig.2). A number of studies have revealed favorable effects of DHA towards visual acuity and neural development, especially for infants.[3-6] Meanwhile, DHA is known as a protector against coronary heart diseases, lowering blood pressure and retarding the development of cardiovascular pathologies. DHA has also been reported to possess desirable preventive effects on Alzheimer's disease,[7] diabetes[8] and cancer.[9]

With the increased understanding of its beneficial health-promoting effects, DHA has become a popular nutrient in recent years. Both DHA-containing nutraceuticals and DHA-fortified functional foods have been marketed to meet the rising demand of DHA supplementation.

BENEFICIAL EFFECTS OF DHA

Visual development

DHA constitutes about 45% of phosphoglycerides in the retina of mammalian species and is especially rich in synaptic regions and disk membranes of photoreceptors [10] It has been indicated that the light sensitivity of retinal rod photoreceptors is dramatically decreased in newborns with the deficiency of n-3 fatty acid, and DHA could significantly promote visual acuity maturation,[5] which may be associated with its direct impact on gene expression critical to retinal function and survival.[11,12]

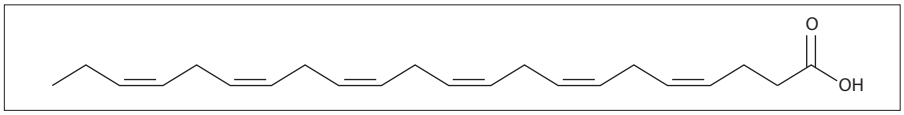


Figure 1. *Structure of Docosahexanoic acid (DHA, C22:6 n-3)*

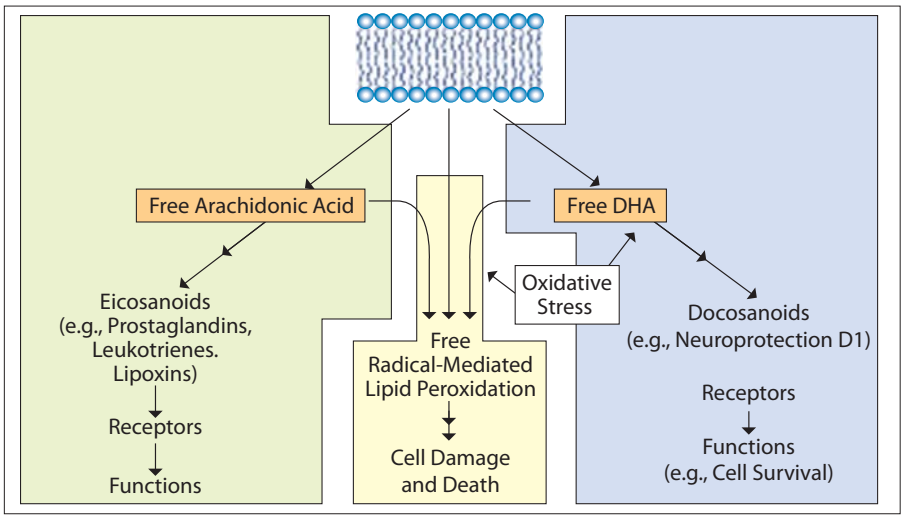


Figure 2. *The lipid bilayer (top of diagram) that constitutes neuronal cell membranes consists largely of phospholipids, such as phosphatidylcholine and phosphatidylserine. One of the principal fatty acids of which the phospholipids are composed is DHA. Under conditions of neuronal stress, especially oxidative stress, free DHA (an omega-3 fatty acid) and arachidonic acid (an omega-6 fatty acid) are released into the neurons, where they undergo the metabolic processes shown in the diagram. [Adapted from Bazan NG (2005). Neuroprotection D1 (NPD1): a DHA-derived mediator that protects brain and retina against cell injury-induced oxidative stress. Brain Pathology, 15:159-166.]*

A number of studies have demonstrated effects of DHA on the improvement in visual function. For example, after feeding DHA-containing diets, preterm infants tend to maintain DHA concentrations in plasma and erythrocyte phospholipid at birth levels,[13] and showed higher visual acuity when compared with infants fed formulas without DHA.[14-16] Birch E. E. *et al* also conducted clinical trials focusing on term infants at different ages and found that when taking formulas supplemented with DHA together with arachidonic acid (ARA), infants had significantly better visual function (sweep visual evoked potential acuity) than infants in the control group receiving formulas without DHA/ARA.[17-19] The possible long-term effect of early DHA supply on visual maturation was also observed based on the study of determinants of stereo acuity development and the results suggest that a maternal antenatal diet rich in DHA is related to the increased stereopsis of infants at age 3.5 year.[20] In addition, the effective concentration of DHA in infant formula is recommended at 0.32% of total fatty acids as other higher levels of DHA supplementation (0.64% DHA and 0.96% DHA) didn't cause additional improvement of visual acuity for infants at 12 months of age.[21]

Brain development

During the brain growth spurt which basically happens from the beginning of the third trimester of pregnancy to 18 months after birth,[22] DHA accumulates in brain greatly due to both the growth in brain size and the increase in DHA content,[23] and there is approximate a 30-fold increase in the total amount of DHA (Fig. 3).[24,25] Therefore, the sufficient supply of DHA is essential to maintain the normal development of brain and results of numerous studies have confirmed the importance of DHA to brain development.

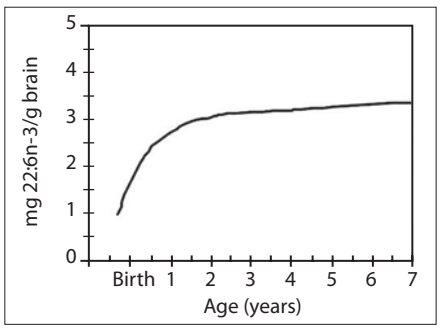


Figure 3. *DHA accretion during the human brain growth spurt [3]*

It was reported that the DHA supplementation could effectively reduce nervousness of preterm infants.[26] Preterm infants fed with DHA-enriched formula demonstrated shorter looking time in the Fagan test of infant intelligence.[27,28] Measures of looking time have been considered as reflecting speed of information processing,[29] thus, infants showing shorter looking times have faster reaction times and may be more efficient to plan a solution and faster to execute it.[30] Infants with impaired attention control were also found to show significantly shorter fixation times after receiving DHA-supplemented formula.[31] Meanwhile, several studies have suggested a beneficial effect of dietary DHA on both intellectual development and cognitive development of infants and children.[32-35]

Pregnant and lactating women are also recommended to have additional intake of DHA which can be transferred to infants.[36,37] It was found that infants of women who supplement DHA during pregnancy or lactation have higher erythrocyte phospholipid DHA when compared to infants of women who breast fed without consuming DHA.[38,39]

Cardioprotective effects

Numerous epidemiological and controlled interventional trials have demonstrated positive effects of DHA in alleviating cardiovascular diseases by a series of mechanisms (Table 1) including preventing arrhytmias,[40] increasing heart rate variability,[41] preventing thrombosis,[42,43] inhibiting atherosclerosis,[44] exerting hypolipidemic effect[45] and anti-inflammatory effect.[46] It was found that higher levels of DHA in circulating blood biomarker due to greater fish intake are capable of reducing risks for the progression of coronary atherosclerosis and lowering risks from sudden cardiac death.[47]

Protective effects on Alzheimer's desease (AD)

DHA plays an important role in neural function. It was reported that administrating with 900 mg/day DHA for 24 weeks would improve learning and memory function in age-related cognitive decline, suggesting that DHA is beneficial in supporting cognitive health with aging.[49] The protective effect against AD of DHA may be largely attributed to two aspects. Firstly, DHA could reduce the production and accumulation of amyloid beta peptide toxin which is thought to cause the disease. On the other hand, DHA is also able to suppress several signal transduction pathways induced by Abeta.[50] Another study found that participants consuming fish once per week at least had 60% less risk of AD when compared with those who ate fish less often, indicating that total intake of n-3 polyunsaturated fatty acids including DHA may decrease the risk of incident AD.[51]

Table 1. Potential mechanisms of cardioprotective effects associated with DHA[48]

Strong antiarrhytmic effect	Reduction in malignant ventricular arrhythmias via enrichment of Cardiac lipids thereby preventing the development of ventricular tachycardia and fibrillation.
Increase in heart rate variability	By increasing parasympathetic tone, inhibition and/or a alteration of cytokine levels, altering the levels of mitogens and other factors.
Antithrombotic effect	Via inhibition of thromboxane A2 in the arachidonic acid cascade, reducing platelet activity, enhancing the production of prostacyclins (pro-vasodialatory) and by lowering postprandial lipemia thereby lowering the pro-coagulant activated factor VII.
Inhibitory effect on atherosclerosis	By regulating plasma cholesterol concentrations, by inhibiting monocyte migration into the plaque and through stimulation of endothelial production of nitric oxide.
Hypolipidemic effect	Lower plasma cholesterol and triacylglycerol concentrations by inhibiting triacylglycerol and very low density lipo-proteins (VLDL) synthesis in liver and by stimulating the synthesis of membrane phospholipids. This also aids in preventing obesity related problems.
Antiinflammatory effect	Through inhibition of smooth cell proliferation, altered eicosanoid synthesis (especially PGE2 and LTB4) and by reducing the expression of cell adhesion molecules. By salvaging cardiomyocytes from hypoxia/re-oxygenation induced damage.

Antidiabetes

DHA and EPA were found to stimulate the secretion of glucagon-link peptide-1 (GLP-1) which is a gut-derived peptide secreted from intestinal cells and considered as a promosing diabetic medicine, indicating that the colon-specific delivery of DHA and EPA might be a novel therapeutic approach for diabetes.[52] Also, it was reported that DHA could increase insulin sensitivity and reduce insulin resistance in mice,[8,53] promote an efficient absorption and metabolism of glucose in the absence of insulin.[54,55]

Anticancer

Both epidemiologic and experimental evidence have demonstrated the anticancer activity of DHA. For example, DHA could induce apoptosis in the human pancreatic cancer cell line through rapid intracellular depletion of reduced glutathione (GSH),[56] and cause the apoptosis of gastric cancer cells by inducing the expression of apoptotic genes in gastric cancer cells.[57] it was also reported that cytotoxicity in various human cancer cells was enhanced by DHA via down-regulating superoxide dismutase (SOD) gene expression, thus weakening cellular antioxidant forces.[58] Gleissman *et al* found that DHA exerts cytotoxic effect on neuroblastoma (an embryonal tumor of the sympathetic nervous system) through the production of hydroperoxy fatty acids that accumulate to toxic intracellular levels.[59]

SOURCES OF DHA

DHA is mostly abundant in unicellular phytoplankton and seaweeds, such as microalgae in which DHA can reach more than 35% (w/w) in refined oils.[60-63] In our daily diet, DHA mainly accumulates in marine products (Table 2) and eggs also contain certain amount of DHA (20 mg DHA/ egg).[64]

Table 2. Aquatic resources rich in DHA (as mol%) content[65,66]

Common Name	DHA content (mol%)
Japanese Anchovy	12.5
Atalantic Cod	37.5
Porbeagle shark	29.0
Pacific oyster	20.2
Lemon sole	7.0
Snapper	33.8

Both preterm and term infants are able to synthesize DHA based on the conversion from α-linolenic acid (ALA, 18:3, n-3) through elongation and desaturation[67,68] (Fig. 4).[47,48] However, the conversion rate is extremely low (<0.1%)[69] due to the weak activity of elongation and desaturase enzymes before birth.[70]

In human milk, fatty acids, including DHA concentration, are closely related to maternal diet. For example, DHA level in the breast milk from vegans and vegetarians are lower than that from omnivores.[72] Low fish consumers have relatively lower levels of DHA in their breast milk than high fish consumers (Table 3).

DHA FROM FISH OIL AND MICROALGAE OIL

Fish oil has been a traditional and important source of long chain polyunsaturated fatty acids including DHA and eicosapentaenoic acid (EPA, 20:5, n-3), which exert desirable effects on preventing cardiovascular diseases and Alzheimer's disease, making it a popular nutraceutical around the world. However, there are two major problems in consuming fish oil: safety/toxicity and sustainability.[73] With the development of industrialization, oceans and waterways have become more contaminated. Mercury and polychlorinated biphenyls levels increase in fish, which are not acceptable to certain consumers, especially children and pregnant women, who are very sensitive to even low amounts of these contaminants.[74,75] For the sustainability issues, there is a sharp decline in the fish populations in parts of the world caused by overfishing and the rapid development of fishing industry has threatened ocean ecosystem and planetary balance.[76] Considering the potential drawbacks of fish oil, it is suggested to obtain omega-3 fatty acids including DHA from microalgae, which are at the bottom of food chain and original provider of DHA.[77] Though some algae species (such as blue-green algae) contain neurotoxins causing neurodegenerative diseases, several DHA-rich algae species including *Schizochytrium , Ulkenia amoeboida and Crypthecodinium cohnii* [62,63] have allowed for commercial use in food industry in many countries (Table 4) with low risks of ocean contaminants based on heterotrophic production.[62,63] Therefore, DHA from microalgae oil is a more sustainable option which is free of environmental pollutants.

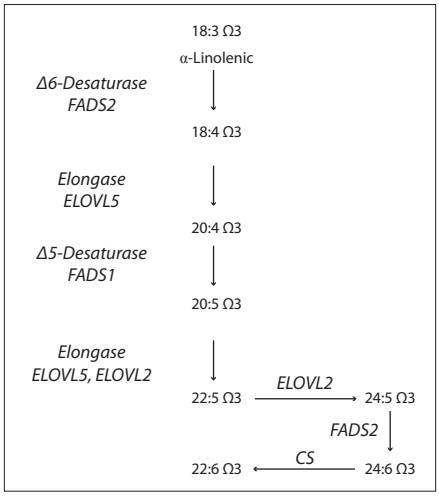


Figure 4. *Metabolic conversion of ALA to DHA[71]*

RECOMMENDED INTAKE OF DHA

So far, there is not a definite international authority regulation on the daily intake of DHA for different people. However, anthorities of various countries have suggested daily intake of DHA towards specific people (Table 5).

Table 3. The fatty acid composition (%) of human milk in relation to maternal diet (data are adopted from the literature)[3]

	Vancouver women (*n* = 12)	Canadian Innuits (*n* = 5)	High fish consumers 17.3±2.1 meals/month (*n* = 6)	Low fish consumers 1.0±1.1 meals/month (*n* = 7)	Danish women (*n* = 45)	Omnivores (*n* = 21)	British Caucasian vegetarians (*n* = 15)	Vegans (*n* = 19)
SFA	43.4	38.2	41.2±3.9	44.7±1.9	43.1±3.8	41.4	38.3	38.3
MUFA	40.5	44.7	38.8±3.1	37.9±2.7	37.7±2.9	42.1	38.2	33.6
18:2*n*-6	12.7±1.8	11.5±0.7	11.4±2.2	9.2±2.8	10.8±2.6	10.9±1.0	19.5±3.6	23.8±1.4
18:3*n*-6	0.6±0.2	0.5±0.2	1.20±0.28	0.73±0.14	1.09±0.39	0.50±0.06	1.25±0.22	1.36±0.18
20:2*n*-6	0.4±0.1	0.2±0.0	0.24±0.03	0.16±0.05	0.21±0.05			
20:3*n*-6			0.29±0.08	0.28±0.04	0.29±0.07	0.40±0.08	0.42±0.07	0.44±0.03
20:4*n*-6	0.7±0.0	0.6±0.0	0.41±0.07	0.37±0.03	0.39±0.07	0.35±0.03	0.38±0.05	0.32±0.02
20:5*n*-3	0.2±0.2	1.1±0.3	0.14±0.06	0.08±0.04	0.10±0.07			
22:5*n*-3	0.4±0.1	0.8±0.2	0.25±0.07	0.17±0.03	0.19±0.09			
22:6*n*-3	0.4±0.1	1.4±0.4	0.53±0.18	0.27±0.12	0.35±0.19	0.37±0.07	0.30±0.05	0.14±0.06
n-6/*n*-3	8.8	3.8	5.6±1.4	8.0±3.7	6.8±2.4	13.5	13.0	16.4

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids.

Table 4. DHA products made by heterotrophic microalgae

Company	Species	Products
Runke (China)	*Crythecodinium cohnii, Schizochytrium* sp.	DHA additives in infant formula and common foods, DHA supplements
Martek (USA)	Crythecodinium cohnii	DHA additves in infant formula and common foods, DHA supplements
Omega Tech (USA)	*Schizochytrium sp.*	Feed
Bio-Marine (USA)	*Schizochytrium sp.*	Feed
Nutrinova (Germany)	*Ulkenia*	Health food

Table 5. Recommended DHA daily intake

Age Range	DHA Daily Intake
Infants	10-12 mg/kg for 6-24 months (WHO)[78] 100mg for 7-24 months (EFSA)[79]
Children and adolescents	110-220 mg (EFSA)[79] 150-200mg (HCN)[80]
Adults	220 mg (NIH & ISSFAL)[81]
Pregnant and lactating women	300 mg (NIH & ISSFAL)[81]

Notes: WHO: World Health Organization
EFSA: European Food Safety Authority
HCN: Health Council of the Netherlands
NIH: National Institute of Health
ISSFAL: International Society for the Study of Fatty Acids

APPLICATION PROGRESS OF DHA

Since DHA is known as involved in health promotion and disease prevention, a variety of DHA-containing products are marketed to fulfill the increasing requirement from consumers. Nowadays, DHA-supplementing products can be divided into two types: nutraceuticals and functional foods.

As nutraceuticals, DHA products are present in the form of soft capsules together with other fatty acids from fish oil/ microalgae oil. Normally, fish oil capsules contain 120-240 mg DHA/capsule, which are usually recommended for adults with hyperglycaemia to lower blood pressure and reduce blood clotting. Compared to fish oil capsules, microalgae oil capsules are more expensive, and there are two major dosages in DHA content: 100 mg/ capsule and 200 mg/ capsule, which are special for infants, children and women at pregnancy and breast-feeding.[73]

In addition, the incorporation of DHA into a series common food leads to the rapid development of functional foods rich in DHA based on advanced and newer food technologies (especially microencapsulation). A number of foods are successfully fortified with DHA and appear in the marketplace, such as breads, cereal bars, infant formulas, milk products, meats and beverages.[82]

CONCLUSION

As an important n-3 polyunsaturated fatty acid, DHA shows diverse health benefits, such as promoting visual and brain development (specific for infants and children), preventing cardiovascular diseases and age-related cognitive decline, exhibiting antidiabetes and anticancer effects. In daily diet, DHA is mainly rich in seafoods including various ocean fish, thus limiting DHA intake to some extent. Therefore, a number of DHA-rich supplements or functional foods have emerged in marketplace. So far, there are two substantial sources for DHA: fish oil and microalgae oil. Considering the safety and sustainability issues towards fish oil, more attention has shifted to more expensive microalgae oil. Whatever the source, DHA-containing products should focus on the stability of DHA which is fragile and easily oxidized by heat, air, water and certain metal ions, leading to unpleasant smell and toxin oxidative derivatives, such as aldehydes and ketons. With the continuous understanding of DHA, the development of DHA-rich supplements and DHA -fortified foods has become a new trend in food industry.

Author's background
***Dr. PENG Xiaofang Becky**, received her PhD degree from the Hong Kong University and is working currently as a Postdoctoral Fellow in City University of Hong Kong. She is a food analytical scientist. **Dr. CHEUNG Hon-Yeung**, who is an associate professor of Pharmaceutics at the City University of Hong Kong, is a manufacturing pharmacist and biotechnologist. He has more than 30 years of working experiences in industries, academic and consultancy jobs. His email address: bhhonyun@cityu.edu.hk*

References

1. Makrides M, Neumann MA , Byard RW *et al.* (1994). Fatty acid composition of brain, retina, and erythrocytes in breast- and formula-fed infants. *Am J Clin Nutr*, 60:189-194.
2. Martin RE, Bazan NG. (1992). Changing fatty acid content of growth cone lipids prior to synaptogenesis. *J Neurochem*, 59:318-325.
3. Lauritzen L, Hansen HS, Jorgensen MH *et al.* (2001). The essentiality of long chain n-3 fatty acids in relation to development and function of the brain and retina. *Prog Lipid Res*, 40:1-94.
4. Ryan AS, Astwood JD, Gautier S *et al.* (2010). Effects of long-chain polyunsaturated fatty acid supplementation on neurodevelopment in childhood: a review of human studies. *Prostaglandins Leukot Essent Fatty Acids*, 82:305-314.
5. Uauy R, Hoffman DR, Peirano P *et al.* (2001). Essential fatty acids in visual and brain development. *Lipids*, 36:885-895.
6. Carlson SE. (2001). Docosahexaenoic acid and arachidonic acid in infant development. *Semin Neonatol*, 6:437-449.
7. Huang TL. (2010). Omega-3 fatty acids, cognitive decline, and Alzheimer's disease: a critical review and evaluation of the literature. *J Alzheimers Dis*, 21:673-690.
8. Vemuri M, Kelley DS, Mackey BE *et al.* (2007). Docosahexaenoic Acid (DHA) But Not Eicosapentaenoic Acid (EPA) Prevents Trans-10, Cis-12 Conjugated Linoleic Acid (CLA)-Induced Insulin Resistance in Mice. *Metab Syndr Relat Disord*, 5:315-322.
9. Kato T, Kolenic N ,Pardini RS. (2007). Docosahexaenoic acid (DHA), a primary tumor suppressive omega-3 fatty acid, inhibits growth of colorectal cancer independent of p53 mutational status. *Nutr Cancer,* 58:178-187.
10. Anderson RE, Maude MB ,Zimmerman W. (1975). Lipids of ocular tissues--X. Lipid composition of subcellular fractions of bovine retina. *Vision Res,* 15:1087-1090.
11. Rotstein NP, Politi LE ,Aveldano MI. (1998). Docosahexaenoic acid promotes differentiation of developing photoreceptors in culture. *Invest Ophthalmol Vis Sci*, 39:2750-2758.
12. Rodriguez de Turco EB, Deretic D, Bazan NG *et al.* (1997). Post-Golgi vesicles cotransport docosahexaenoyl-phospholipids and rhodopsin during frog photoreceptor membrane biogenesis. *J Biol Chem,* 272:10491-10497.
13. Boehm G, Borte M, Bohles HJ *et al.* (1996). Docosahexaenoic and arachidonic acid content of serum and red blood cell membrane phospholipids of preterm infants fed breast milk, standard formula or formula supplemented with n-3 and n-6 long-chain polyunsaturated fatty acids. *Eur J Pediatr,* 155:410-416.
14. Carlson SE, Werkman SH, Rhodes PG *et al.* (1993). Visual-acuity development in healthy preterm infants: effect of marine-oil supplementation. *Am J Clin Nutr,* 58:35-42.
15. Carlson SE, Werkman SH, Tolley EA. (1996). Effect of long-chain n-3 fatty acid supplementation on visual acuity and growth of preterm infants with and without bronchopulmonary dysplasia. *Am J Clin Nutr,* 63:687-697.
16. O'Connor DL, Hall R, Adamkin D *et al.* (2001). Growth and development in preterm infants fed long-chain polyunsaturated fatty acids: a prospective, randomized controlled trial. *Pediatrics,* 108:359-371.
17. Birch EE, Castaneda YS, Wheaton DH *et al.* (2005). Visual maturation of term infants fed long-chain polyunsaturated fatty acid-supplemented or control formula for 12 mo. *Am J Clin Nutr*, 81:871-879.
18. Birch EE, Garfield S, Castaneda Y *et al.* (2007). Visual acuity and cognitive outcomes at 4 years of age in a double-blind, randomized trial of long-chain polyunsaturated fatty acid-supplemented infant formula. *Early Hum Dev*, 83:279-284.

19. Birch EE, Garfield S, Hoffman DR *et al.* (2000). A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. *Dev Med Child Neurol,* 42:174-181.

20. Williams C, Birch EE, Emmett PM *et al.* (2001). Stereoacuity at age 3.5 y in children born full-term is associated with prenatal and postnatal dietary factors: a report from a population-based cohort study. *Am J Clin Nutr,* 73:316-322.

21. Birch EE, Carlson SE, Hoffman DR *et al.* (2010). The DIAMOND (DHA Intake And Measurement Of Neural Development) Study: a double-masked, randomized controlled clinical trial of the maturation of infant visual acuity as a function of the dietary level of docosahexaenoic acid. *Am J Clin Nutr*, 91:848-859.

22. Dobbing J, Sands J. (1979). Comparative aspects of the brain growth spurt. *Early Hum Dev*, 3:79-83.

23. Dobbing J, Sands J. (1973). Quantitative growth and development of human brain. *Arch Dis Child*, 48:757-767.

24. Martinez M. (1992). Abnormal profiles of polyunsaturated fatty acids in the brain, liver, kidney and retina of patients with peroxisomal disorders. *Brain Res*, 583:171-182.

25. Martinez M. (1994). Polyunsaturated fatty acids in the developing human brain, red cells and plasma: influence of nutrition and peroxisomal disease. *World Rev Nutr Diet,* 75:70-78.

26. Vanderhoof J, Gross S, Hegyi T *et al.* (1999). Evaluation of a long-chain polyunsaturated fatty acid supplemented formula on growth, tolerance, and plasma lipids in preterm infants up to 48 weeks postconceptional age. *J Pediatr Gastroenterol Nutr,* 29:318-326.

27. Werkman SH, Carlson SE. (1996). A randomized trial of visual attention of preterm infants fed docosahexaenoic acid until nine months. *Lipids*, 31:91-97.

28. Carlson SE, Werkman SH. (1996). A randomized trial of visual attention of preterm infants fed docosahexaenoic acid until two months. *Lipids,* 31:85-90.

29. Rose SA, Feldman JF. (1997). Memory and speed: their role in the relation of infant information processing to later IQ. *Child Dev*, 68:630-641.

30. Jacobson SW, Jacobson JL, O'Neill JM *et al.* (1992). Visual expectation and dimensions of infant information processing. *Child Dev,* 63:711-724.

31. Willatts P, Forsyth JS, DiModugno MK *et al* In *Major controversies in infant nurition*; David, T. J., Ed.; RSM Press: London, 1996, p 57-70.

32. Yoshida S, Sato A, Okuyama H. (1998). Pathophysiological effects of dietary essential fatty acid balance on neural systems. *Jpn J Pharmacol*, 77:11-22.

33. Florey CD, Leech AM, Blackhall A. (1995). Infant feeding and mental and motor development at 18 months of age in first born singletons. *Int J Epidemiol*, 24 Suppl 1:S21-26.

34. Lucas A, Morley R, Cole TJ *et al.* (1994). A randomised multicentre study of human milk versus formula and later development in preterm infants. *Arch Dis Child Fetal Neonatal Ed*, 70:F141-146.

35. Rogan WJ, Gladen BC. (1993). Breast-feeding and cognitive development. *Early Hum Dev,* 31:181-193.

36. Smithers LG, Gibson RA, McPhee A *et al.* (2008). Effect of two doses of docosahexaenoic acid (DHA) in the diet of preterm infants on infant fatty acid status: results from the DINO trial. *Prostaglandins Leukot Essent Fatty Acids,* 79:141-146.

37. Harris WS, Connor WE, Lindsey S. (1984). Will dietary omega-3 fatty acids change the composition of human milk? *Am J Clin Nutr*, 40:780-785.

38. Connor WE, Lowensohn R, Hatcher L. (1996). Increased docosahexaenoic acid levels in human newborn infants by administration of sardines and fish oil during pregnancy. *Lipids,* 31 Suppl:S183-187.

39. Gibson RA, Neumann MA, Makrides M. (1997). Effect of increasing breast milk docosahexaenoic acid on plasma and erythrocyte phospholipid fatty acids and neural indices of exclusively breast fed infants. *Eur J Clin Nutr*, 51:578-584.

40. Kang JX, Leaf A. (1996). Antiarrhythmic effects of polyunsaturated fatty acids. Recent studies. *Circulation*, 94:1774-1780.

41. Christensen JH, Schmidt EB. (2007). Autonomic nervous system, heart rate variability and n-3 fatty acids. *J Cardiovasc Med (Hagerstown)*, 8 Suppl 1:S19-22.

42. Schmidt EB. (2003). Marine n-3 fatty acids and thrombosis. *Thromb Res*, 111:9-10.

43. Andriamampandry MD, Leray C, Freund M *et al.* (1999). Antithrombotic effects of (n-3) polyunsaturated fatty acids in rat models of arterial and venous thrombosis. *Thromb Res,* 93:9-16.

44. von Schacky C, Angerer P, Kothny W *et al.* (1999). The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med,* 130:554-562.

45. Elvevoll EO, Eilertsen KE, Brox J *et al.* (2008). Seafood diets: hypolipidemic and antiatherogenic effects of taurine and n-3 fatty acids. *Atherosclerosis,* 200:396-402.

46. Calder PC. (2003). Long-chain n-3 fatty acids and inflammation: potential application in surgical and trauma patients. *Braz J Med Biol Res*, 36:433-446.

47. Holub BJ. (2009). Docosahexaenoic acid (DHA) and cardiovascular disease risk factors. *Prostaglandins Leukot Essent Fatty Acids,* 81:199-204.

48. Narayan B, Miyashita K, Hosakawa M. (2006). Physiological effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)-a review. *Food Reviews International,* 22:291-307.

49. Yurko-Mauro K, McCarthy D, Rom D *et al.* (2010). Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. *Alzheimers Dement,* 6:456-464.

50. Cole GM, Ma QL, Frautschy SA. (2009). Omega-3 fatty acids and dementia. *Prostaglandins Leukot Essent Fatty Acids,* 81:213-221.

51. Morris MC , Evans DA , Bienias JL *et al.* (2003). Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch Neurol,* 60:940-946.

52. Morishita M, Tanaka T, Shida T *et al.* (2008). Usefulness of colon targeted DHA and EPA as novel diabetes medications that promote intrinsic GLP-1 secretion. *J Control Release,* 132:99-104.

53. Shimura T, Miura T, Usami M *et al.* (1997). Docosahexanoic acid (DHA) improved glucose and lipid metabolism in KK-Ay mice with genetic non-insulin-dependent diabetes mellitus (NIDDM). *Biol Pharm Bull*, 20:507-510.

54. Popp-Snijders C, Schouten JA, Heine RJ *et al.* (1987). Dietary supplementation of omega-3 polyunsaturated fatty acids improves insulin sensitivity in non-insulin-dependent diabetes. *Diabetes Res*, 4:141-147.

55. Storlien LH, Kraegen EW, Chisholm DJ *et al.* (1987). Fish oil prevents insulin resistance induced by high-fat feeding in rats. *Science,* 237:885-888.

56. Merendino N, Molinari R, Loppi B *et al.* (2003). Induction of apoptosis in human pancreatic cancer cells by docosahexaenoic acid. *Ann N Y Acad Sci,* 1010:361-364.

57. Lee SE, Lim JW, Kim H. (2009). Activator protein-1 mediates docosahexaenoic acid-induced apoptosis of human gastric cancer cells. *Ann N Y Acad Sci,* 1171:163-169.

58. Tuller ER, Beavers CT, Lou JR *et al.* (2009). Docosahexaenoic acid inhibits superoxide dismutase 1 gene transcription in human cancer cells: the involvement of peroxisome proliferator-activated receptor alpha and hypoxia-inducible factor-2alpha signaling. *Mol Pharmacol*, 76:588-595.

59. Gleissman H, Yang R, Martinod K *et al.* (2010). Docosahexaenoic acid metabolome in neural tumors: identification of cytotoxic intermediates. *Faseb J*, 24:906-915.

60. Doughman SD, Krupanidhi S, Sanjeevi CB. (2007). Omega-3 fatty acids for nutrition and medicine: considering microalgae oil as a vegetarian source of EPA and DHA. *Curr Diabetes Rev*, 3:198-203.

61. Hammond BG, Mayhew DA, Naylor MW *et al.* (2001). Safety assessment of DHA-rich microalgae from Schizochytrium sp. *Regul Toxicol Pharmacol*, 33:192-204.

62. Sijitsma L, Anderson AJ, Ratledge C In *Single cell oils*; Ratledge, C., Cohen, Z., Eds.; AOCS:2005.

63. Thomas K, Matthias R, Fabritius D In *Single cell oils*; Ratledge, C., Cohen, Z., Eds.; AOCS: 2005.

64. Sanders TA. (2009). DHA status of vegetarians. *Prostaglandins Leukot Essent Fatty Acids,* 81:137-141.

65. Toyoshima K, Noguchi R, Hosokawa M *et al.* (2004). Separation of sardine oil without heating from surimi waste and its effect on lipid metabolism in rats. *J Agric Food Chem*, 52:2372-2375.

66. Youdim KA, Martin A, Joseph JA. (2000). Essential fatty acids and the brain: possible health implications. *Int J Dev Neurosci,* 18:383-399.

67. Salem N, Jr., Wegher B, Mena P *et al.* (1996). Arachidonic and docosahexaenoic acids are biosynthesized from their 18-carbon precursors in human infants. *Proc Natl Acad Sci U S A*, 93:49-54.

68. Sauerwald TU, Hachey DL, Jensen CL *et al.* (1997). Intermediates in endogenous synthesis of C22:6 omega 3 and C20:4 omega 6 by term and preterm infants. *Pediatr Res,* 41:183-187.

69. Williams CM, Burdge G. (2006). Long-chain n-3 PUFA: plant v. marine sources. *Proc Nutr Soc*, 65:42-50.

70. Uauy R, Mena P, Wegher B *et al*. (2000). Long chain polyunsaturated fatty acid formation in neonates: effect of gestational age and intrauterine growth. *Pediatr Res,* 47:127-135.

71. Koletzko B, Larque E, Demmelmair H. (2007). Placental transfer of long-chain polyunsaturated fatty acids (LC-PUFA). *J Perinat Med*, 35 Suppl 1:S5-11.

72. Sanders TA, Reddy S. (1992). The influence of a vegetarian diet on the fatty acid composition of human milk and the essential fatty acid status of the infant. *J Pediatr*, 120: S71-77.

73. Cannon D. (2009). From fish oil to microalgae oil ... A win-win shift for humans and our habitat. *Explore (NY),* 5:299-303.

74. Yin X, Sun L, Zhu R *et al.* (2007). Mercury-selenium association in antarctic seal hairs and animal excrements over the past 1,500 years. *Environ Toxicol Chem,* 26:381-386.

75. Budtz-Jorgensen E, Grandjean P, Weihe P. (2007). Separation of risks and benefits of seafood intake. *Environ Health Perspect,* 115:323-327.

76. Worm B, Barbier EB, Beaumont N *et al.* (2006). Impacts of biodiversity loss on ocean ecosystem services. *Science*, 314:787-790.

77. Harris WS. (2004). Fish oil supplementation: evidence for health benefits. *Cleve Clin J Med*, 71:208-210, 212, 215-208 passim.

78. In *The joint FAO/WHO expert consultation on fats and fatty acids in human nutrition* Geneva, 2008.

79. Authority EFS. (2010). Scientific opinion on dietary reference values for fats, including saturated fatty acids, polyunsaturated fatty acids, monounsatureated fatty acids, trans fatty acids, and cholesterol. *EFSA Journal,* 8:1461-1566.

80. Netherlands, H. C. o. t., Ed. Hague, 2006.

81. Simopoulos AP, Leaf A, Salem N, Jr. (1999). Workshop on the Essentiality of and Recommended Dietary Intakes for Omega-6 and Omega-3 Fatty Acids. *J Am Coll Nutr,* 18:487-489.

82. Whelan J, Rust C. (2006). Innovative dietary sources of n-3 fatty acids. *Annu Rev Nutr,* 26:75-103.

Urinary Tract Infection

LAI, Oi-Lun Ellen
Queen Mary Hospital, Pokfulam, Hong Kong SAR, China

ABSTRACT

Symptomatic urinary tract infections (UTIs) are among the most common bacterial infections. Cystitis and pyelonephritis are the most common urinary tract infections. They are predominant in females than in males. The most important organism in the pathophysiology of UTI is Escherichia coli, which accounts for approximately 80% of UTIs. A 3-day trimethoprim-sulfamethoxazole (TMP-SMX) is the standard of care for treatment of uncomplicated cystitis in healthy non-pregnant adult woman. Three-day fluoroquinolones can be considered in areas with E. coli resistance to TMP-SMX more than 20% and in patients with sulfonamide allergy. Due to their broader antimicrobial spectra, widespread use of fluoroquinolones may be associated with increased bacterial resistance. Beta-lactam antibiotics including penicillins and cephalosporins are effective treatments for UTI but a 5-7 day course is recommended. Nitrofurantoin is less well studied in clinical trials, and a 5 to 7-day course is required for effective treatment. Fosfomycin offers a convenient single-dose treatment course but its use is limited by the high drug cost. For UTIs in pregnancy, beta-lactam antibiotics and nitrofurantoin are safe and effective choices. TMP-SMX and fluoroquinolones are not recommended. Little evidence exists for fosfomycin although it appears to be safe. TMP-SMX has been shown to be effective for prophylaxis against recurrent UTIs. Other antibiotics are probably effective. Postcoital TMP-SMX has also been shown in a single study to reduce UTIs that are suspected to be related to sexual activity.

Keywords: *Urinary tract infection, cystitis, pyelonephritis, bacteriuria*

INTRODUCTION

Urinary tract infection (UTI) is an infection that affects any part of the urinary tract. It covers a spectrum of infections including uncomplicated lower UTI, complicated UTIs, upper UTIs (pyelonephritis), nosocomial UTIs and catheter-associated UTIs.

Uncomplicated UTIs are not associated with structural or neurologic abnormalities that may affect the normal urine flow or voiding mechanisms. Complicated UTIs, on the other hand, result from abnormalities from the urinary tract (e.g. congenital abnormality, urinary stones, indwelling catheters, prostatic hypertrophy) that predisposes patients to UTIs.

Lower UTIs include cystitis (bladder), urethritis (urethra), prostatitis (prostate gland), and epididymitis (epididymis). Upper UTIs involve the ureters and the kidney parenchyma and are more commonly referred to as pyelonephritis.

In this article, focus is put on uncomplicated lower UTIs and pyelonephritis in women. UTIs in males, catheter-related UTIs, and UTIs in pediatrics will be addressed in brief.

PATHOPHYSIOLOGY AND MICROBIOLOGY

Approximately 50-60% of adult women report that they have had a UTI at some time during their life.[1] Young sexually active women have approximately 0.5 episodes of acute cystitis per person-year, suggesting that many millions of episodes of acute cystitis probably occur annually among women in the United States.[2]

UTIs can be acquired via three possible routes: the ascending, hematogenous, or lymphatic pathways. In females, the short urethra and the proximity of the uretural opening to the perirectal area makes colonization of the urethra likely. Bacteria are then believed to ascend to the bladder via the urethra, causing cystitis. Pyelonephritis occurs in a similar retrograde ascending fashion from the bladder, but it may occur hematogenously.

The bacteria causing uncomplicated UTIs usually originate from the bowel flora of the host. A review of 2409 women with acute cystitis in six randomized trials revealed that in 79% were due to *Escherichia coli.*[3] The major remaining pathogens were Staphylococcus saprophyticus (4.4%), Klebsiella pneumoniae (4.3%), and Proteus mirabilis (3.7%). Citrobacter and Enterococci are occasional causes of UTI in these patients.

SIGNS AND SYMPTOMS

Dysuria, difficulty and/or painful micturition, are the major symptoms of lower UTIs that indicate mucosal inflammation of the lower urinary tract. Other signs and symptoms include hematuria, suprapubic discomfort, frequency, urgency, and nocturia.

The signs and symptoms of pyelonephritis on presentation may vary, including fever, rigor, shaking chills, costovertebral angle tenderness, loin/flank pain, anorexia, nausea, and vomiting. Patients with urosepsis may present with septic shock.

DIAGNOSIS

In women who present with 1 or more symptoms of UTI, the probability of infection is approximately 50%. Specific combinations of symptoms (eg, dysuria and frequency without vaginal discharge or irritation) raise the probability of UTI to more than 90%, effectively ruling in the diagnosis based on history alone. In contrast, history taking, physical examination, and dipstick urinalysis are not able to reliably lower the post-test probability of disease to a level where a UTI can be ruled out when a patient presents with 1 or more symptoms.[4]

Urine culture is very useful for determination of the identity of the infecting microorganism(s) and for antimicrobial susceptibility testing. This is particularly important in areas with increasing incidence of antimicrobial resistance. Urine cultures are also necessary for outpatients who have recurrent UTIs, experience treatment failures, complicated UTIs, and inpatients with UTIs. Significant bacteriuria, commonly defined as the presence of 100,000 colony-forming units (CFU) per milliliter of urine obtained via the clean-catch midstream technique is the most commonly used criterion. Most patients with UTIs, however, do not fall into this category, and 30-50% of patients with acute urethral syndrome will have colony counts of <100,000 CFU/mL.[5] For this reason, some laboratories have opted to use lower colony counts as a criterion for interpreting and reporting results. One common criterion is a colony count of 10,000 CFU/mL, which would be expected to increase the sensitivity of the test while retaining the practicality of the test to clinicians and laboratories. For urine culture specimens obtained via suprapubic aspirate or catheterization, the most appropriate diagnostic criterion is a bacterial concentration of not less than 100 CFU/mL.[6]

ASYMPTOMATIC BACTERIURIA AND SYMPTOMATIC ABACTERIURIA

Asymptomatic bacteriuria (ASB) refers to the presence of a positive urine culture (significant bacteriuria, >100,000 CFU/ml) in a patient lacking symptoms of a UTI. Screening of asymptomatic subjects for bacteriuria is appropriate if bacteriuria has adverse outcomes that can be prevented by antimicrobial therapy. The diagnosis of asymptomatic bacteriuria should be based on culture of a urine specimen collected in a manner that minimizes contamination.

- For asymptomatic women, bacteriuria is defined as 2 consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts of 100,000 CFU/mL.
- A single, clean-catch, voided urine specimen with 1 bacterial species isolated in a quantitative count of 100,000 CFU/mL identifies bacteriuria in asymptomatic men.
- A single catheterized urine specimen with 1 bacterial species isolated in a quantitative count of 100 CFU/mL identifies bacteriuria in women or men.

Antimicrobial therapy in the male and non-pregnant female with asymptomatic bacteriuria is controversial; it is believed that treatment has little effect on the natural course of infections. Pyuria accompanying asymptomatic bacteriuria is not an indication for antimicrobial treatment. In contrast, screening and treatment for a positive culture is recommended in pregnancy even if the patient is asymptomatic (see "UTI in pregnancy"). Screening for and treatment of asymptomatic bacteriuria is recommended before transurethral resection of the prostate and before other urologic procedures for which mucosal bleeding is anticipated.[7]

On the other hand, symptomatic abacteriuria, also known as the acute urethral syndrome, is seen in patients who do not have significant bacteriuria but who have UTI symptoms (frequency, urgency dysuria). It is important to rule out other causes of the acute urethral syndrome. One study performed suprapubic aspirate in women with acute urethral syndrome and considered any bacteria present in this uncontaminated specimen to represent infection.[8] Among 42 women (most of whom had 100 CFU/mL on culture of a midstream specimen) who also had pyuria, 27 had a positive aspirate culture: 24 *E. coli*; and 3 S. saprophyticus. Among women without bladder bacteriuria but with pyuria, 10 of 16 had Chlamydia trachomatis. All of these women responded to appropriate antimicrobial therapy with resolution of symptoms. In comparison, none of 15 women with similar symptoms but no pyuria had a positive bladder aspirate culture.

In women with acute urethral syndrome and pyuria, single-dose or short-course therapy with trimethoprim–sulfamethoxazole has been used effectively, and prolonged courses of therapy are not necessary for the majority of patients. If single-dose or short-course therapy is ineffective, a culture should be obtained. If the patient reports recent sexual activity, therapy for C. trachomatis should be considered (azithromycin 1 g orally as a single dose or doxycycline 100 mg twice daily orally for 7 days).

TREATMENT OVERVIEW OF ACUTE UNCOMPLICATED LOWER UTIS IN FEMALES

Treatment of all symptomatic and selected asymptomatic patients with bacteriuria is important to eradicate the invading organism, prevent or treat systemic consequences of infection, and prevent recurrence of infection. Empirical antibiotic therapy for acute uncomplicated bacterial cystitis is illustrated below:

1. Sulfonamides and trimethoprim

Sulfamethoxazole interferes with bacterial folic acid synthesis and growth via inhibition of dihydrofolic acid formation from para-aminobenzoic acid; trimethoprim inhibits dihydrofolic acid reduction to tetrahydrofolate resulting in sequential inhibition of enzymes of the folic acid pathway. Both are excreted in urine as metabolites and unchanged drug.

Sulfamethoxazole-trimethoprim (TMP-SMX) is active against common urinary tract pathogens, both aerobic gram-positive and gram-negative bacteria, except Pseudomonas aeruginosa. TMP-SMX is approved for treatment of urinary tract infections due to *E. coli*, Klebsiella and Enterobacter sp, *M. morganii, P. mirabilis* and *P. vulgaris*; while trimethoprim alone is approved for the treatment of UTIs due to susceptible strains of *E. coli, P. mirabilis, K. pneumoniae, Enterobacter* sp and coagulase-negative *Staphylococcus* including *S. saprophyticus*.

The 1999 IDSA guideline recommends TMP-SMX or trimethoprim for empirical treatment of acute uncomplicated cystitis in adult non-pregnant women in areas where the prevalence of resistance to these drugs among *E. coli* strains causing cystitis is <20%. For susceptible organisms, TMP-SMX 960mg twice daily orally given for 3 days is highly effective therapy for uncomplicated bacterial cystitis.[9]

TMP-SMX should only be used during pregnancy if the benefit justifies the potential risk. The use of TMP-SMX during pregnancy may increase the risk of congenital anomalies including cardiovascular defects, oral clefts, urinary tract anomalies, and neural tube defects. TMP-SMX is contraindicated in late pregnancy because sulfonamides pass the placenta and may cause kernicterus in the newborn, but this has not been observed specifically with SMX.

2. Fluoroquinolones

Fluoroquinolones, including norfloxacin, ofloxacin, ciprofloxacin and levofloxacin, exhibit bactericidal activity by inhibiting bacterial DNA gyrase, an essential bacterial enzyme that maintains the superhelical structure of DNA that is required for DNA replication and transcription, DNA repair, recombination, and transposition. Fluoroquinolones

possess activity against and gram-negative aerobic organisms, and newer generation fluoroquinolones also have activity against gram-positive organisms are effective in treatment of cystitis and UTIs with structural or functional urinary tract abnormalities and complicated infections. Ciprofloxacin has the greatest activity against Pseudomonas, while levofloxacin shows a slightly lower activity against Pseudomonas and norfloxacin has no anti-pseudomonal activity.

Among the fluoroquinolones used for multiday therapies, ofloxacin is equivalent to TMP-SMX, and norfloxacin, ciprofloxacin are similar to TMP-SMX. Other recently introduced fluoroquinolones are probably as effective. Nevertheless, compared to TMP-SMX, fluoroquinolones are more expensive and provide no additional benefit. Moreover, overuse of respiratory fluoroquinolones (those with activity against *S. pneumoniae*, e.g. levofloxacin) which have broader antimicrobial spectra in UTIs may promote drug resistance, and the resulting emergence of resistance may limit their usefulness for respiratory, polymicrobial, and other non-urinary infections. Fluoroquinolones therefore are not universally recommended as first line empirical therapy of uncomplicated UTIs. Use of fluoroquinolones in UTI may be appropriate when: 1) patient has sulfa allergy, 2) urine culture recovers resistant organisms, 3) there is >20% resistance of E. coli to TMP-SMX in the region.

Oral absorption of fluoroquinolones may be reduced by antacids, iron salts, calcium salts, and zinc salts. Dairy products may also impair the absorption of fluoroquinolones. It is recommended to separate the administration times according to manufacturers' recommendations. Fluoroquinolones have been related to cartilage damage in immature animals, they should only be used during pregnancy if a safer option is not available.

It should be emphasized that moxifloxacin is not licensed for use in UTIs due to inability to achieve adequate urine levels.

3. Nitrofurantoin

Nitrofurantoin is a synthetic nitrofuran that interferes with bacterial carbohydrate metabolism by inhibiting acetylcoenzyme A. It is bactericidal in urine against uropathogens such as *S. saprophyticus*, *E. faecalis*, and *E. coli.* Nitrofurantoin demonstrates a consistently low level of resistance among *E. coli*, gram-positive cocci (including Enterococcus and *S. saprophyticus*), but it possesses no activity against Proteus, Serratia, or Pseudomonas species. It is approved for the prevention and treatment of urinary tract infections caused by susceptible strains of *E. coli, S. aureus*, Enterococcus, Klebsiella, and Enterobacter. Nitrofurantoin should not be used to treat acute pyelonephritis since it does not achieve reliable kidney tissue concentrations.

Nitrofurantoin (macrocrystals 100 mg twice daily for 5 days) is equivalent clinically and microbiologically to TMP-SMX (1 double strength [160/800 mg] tablet twice daily for 3 days) in the treatment of uncomplicated cystitis,

Treatment for acute uncomplicated lower UTIs in non-pregnant females

Drug	Usual adult dosage	Comment	Recommendation rating
Beta-lactam antibiotics			
Amoxicillin	Oral: 250-500 mg every 8 hours.	Broad-spectrum activity. Amoxicillin preferred to ampicillin as oral treatment in uncomplicated UTIs due to better oral absorption. Increasing E coli resistance has limited amoxicillin use. Amoxicillin and amoxicillin-clavulanate are drugs of choice for enterococci sensitive to penicillin. Amoxicillin-clavulanate is preferred for resistance problems. Cephalosporins have no added advantage and are more expensive. Cephalosporins have no activity against enterococci. 7-day treatment is recommended.	E, III
Amoxicillin clavulanate	Oral: Mild to moderate infections: One 375-mg tablet three times daily or 625-mg tablet twice daily. Severe infections Two 375-mg tablet three times daily or one 1-g tablet twice daily.		
Cefuroxime axetil	Oral: 125-250 mg every 12 hours for 7-10 days.		
Cephalexin	Oral: 500 mg every 12 hours for 7-14 days.		
Others			
Fosfomycin trometamol	Oral: single dose 3 g.	Convenient single-dose treatment. Less effective than TMP-SMX or the fluoroquinolones Not reliably effective against S. saprophyticus. Expensive. Not indicated for upper UTIs.	B, I
Nitrofurantoin	Oral: (microcrystalline) 50-100 mg every 6 hours; for 7 days or at least 3 days after obtaining sterile urine. Oral: (macrocrystals) 100 mg twice daily for 7 days.	Cheap. Inactive against Proteus and Pseudomonas species. Not recommended in patients with renal impairment. Effective for prophylaxis. Not indicated for upper UTIs. Gastrointestinal upset is frequent.	B, I
Sulfonamides and trimethoprim			
Trimethoprim	Oral: 100 mg every 12 hours or 200 mg every 24 hours for 3-10 days.	TMP-SMX is the standard treatment for UTIs unless in areas or high resistance or contraindication exists. Effective in 3-day treatment course. TMP-SMX is also effective in complicated and recurrent infections.	A,II
Trimethoprim - sulfamethoxazole	Oral: 960mg every 12 hours for 3-5 days.		A,I
Fluoroquinolones			
Ciprofloxacin	Oral: 250 mg every 12 hours for 3 days. I.V.: 200 mg every 12 hours for 7-14 days.	Ciprofloxacin has better antipseudomonal activity than levofloxacin. Norfloxacin has no activity against pseudomonas. Due to activity against gram-positive Streptococci, extensive use of ofloxacin and levofloxacin may lead to resistance. Also effective for pyelonephritis and prostatitis. 3-day therapy is effective.	A,II
Levofloxacin	Oral, IV: 250 mg every 24 hours for 3 days.		A,II
Norfloxacin	Oral: Due to E. coli, K. pneumoniae, P. mirabilis: 400 mg every 12 hours for 3 days. Due to other organisms: 400 mg every 12 hours for 7-10 days.		A,II
Ofloxacin	Oral: 200 mg every 12 hours for 3-7 days.		A,I

with clinical cure rates 84 and 79% respectively.[10] A 7-day nitrofurantoin may or may not be similar in effectiveness to trimethoprim and TMP-SMX.

It is of note that the dosage for microcrystalline nitrofurantoin is 50-100 mg 4 times daily, compared to the macrocrystalline nitrofurantoin which is 100 mg twice daily. The macrocrystalline form is absorbed more slowly due to slower dissolution and helps to decrease the nausea and vomiting associated with microcrystalline product,[11] but is more expensive. Nitrofurantoin is contraindicated in significant renal impairment (anuria, oliguria, significantly elevated serum creatinine, or creatinine clearance <60 mL/minute), as it will not achieve adequate concentration in urine and is toxic.

4. Beta-lactam antibiotics

Beta-lactams exert bactericidal activity by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls. They are excreted rapidly in the urine, and are as a group less effective in treatment of cystitis than are TMP-SMX, trimethoprim, and the fluoroquinolones when given for 3 days. Among penicillins, ampicillin (and amoxicillin) is the standard penicillin that has broad-spectrum activity including enterococci. Increasing *E. coli* resistance has limited amoxicillin use in acute cystitis. Amoxicillin-clavulanate is preferred for resistance problems.

There are no major advantages of cephalosporins over other agents in the treatment of UTIs, and they are more expensive. Cephalosporins may be useful in cases of resistance to amoxicillin and TMP-SMX according to culture and sensitivity tests. These agents are not active against enterococci.

5. Fosfomycin

Fosfomycin belongs to phosphonic acid derivative. It kills bacteria by inhibiting pyruvyl transferase, which is critical in the synthesis of cell walls by bacteria. It is bactericidal against most UTI pathogens, including *E coli*, Enterobacter, Klebsiella, and Enterococcus species. Little cross-resistance between fosfomycin and other antibacterial agents exists. 38% of fosfomycin is excreted unchanged in the urine, and high urinary levels (100 mcg/mL) persist for more than 48 hours after a single 3-g dose. Fosfomycin (as trometamol salt) is approved by the US Food and Drug Administration (FDA) for the treatment of uncomplicated UTI in women due to susceptible strains of *E. coli* and *Enterococcus faecalis*. It is a unique antibiotic for its single-dose advantage over other antibiotics; nevertheless, cost has limited its use in the treatment of UTI. Same as nitrofurantoin, it should not be used to treat pyelonephritis.

In clinical trials, single-dose treatment with fosfomycin is comparable to a 7-day regimen of nitrofurantoin, but is less effective than a 7 to 10-day course of ciprofloxacin or TMP-SMX.[12] However, single-dose fosfomycin has not been compared with short course therapy of other agents.

DURATION OF TREATMENT IN UNCOMPLICATED CYSTITIS

Single-dose therapy (e.g. TMP-SMX 2 double-strength tablets or amoxicillin 3 grams) for UTIs has been proposed to decrease treatment course, increase compliance, and reduce side effects. In otherwise healthy adult non-pregnant women with acute uncomplicated bacterial cystitis, single-dose therapy of TMP-SMX, trimethoprim, fluoroquinolones is generally less effective than the same antimicrobial used for longer durations. Studies on TMP-SMX, trimethoprim and fluoroquinolones revealed significantly lower eradication rates with single-dose therapy than with longer durations.

On the other hand, most antimicrobials given for 3 days are as effective as the same antimicrobial given for a longer duration, and 3-day regimens are preferable over long course (7 to 10 days) regimens for the treatment of acute uncomplicated cystitis because of better compliance, lower cost, and lower frequency of adverse reactions.

Several studies and clinical experience have confirmed the effectiveness of three-day regimens of trimethoprim, TMP-SMX, or a fluoroquinolone for the treatment of acute uncomplicated cystitis. [13] There is no apparent benefit in extending therapy with TMP-SMX or a fluoroquinolone past three days, and adverse reactions are more common in patients treated with longer regimens.

The effectiveness of a 3-day regimen was also supported by a meta-analysis that included 32 trials (9605 patients).[14] Antibiotic therapy for 3 days was similar to prolonged therapy (5 days) in achieving symptomatic cure, while prolonged treatment was more effective in obtaining bacteriologic cure.

However, in comparison, 3-day regimens with beta-lactams are less effective than 5 or more days of therapy. [15] A 3-day regimen of trimethoprim-sulfamethoxazole is more effective and less expensive than 3-day regimens of nitrofurantoin, cefadroxil, or amoxicillin for treatment of uncomplicated cystitis in women.[16] A 3-day course of amoxicillin-clavulanate was not as effective as ciprofloxacin even in women with susceptible strains.[17]

In general, a 3-day treatment duration is recommended for trimethoprim, TMP-SMX and fluoroquinolones. A 7-day treatment should be allowed for other antibiotics as mentioned above, in pregnancy, or in UTIs with factors associated with occult renal or prostatic involvement and with complication factors.[18] Nevertheless, these guidelines are based on antimicrobial susceptibilities reported in the late 1990s, which are changing over time and vary geographically.

UTI IN PREGNANCY

Because of the physiologic changes associated with pregnancy, pregnant patients are considered immunocompromised UTI hosts. There is an increased risk of serious infectious complications from symptomatic and asymptomatic urinary infections in a healthy pregnant woman. Women identified with asymptomatic bacteriuria in early pregnancy have a 20 to 30-fold increased risk of developing pyelonephritis during pregnancy, compared with women without bacteriuria.[19] These women also are more likely to experience premature delivery and to have infants of low birth weight. Prospective, comparative clinical trials have reported that antimicrobial treatment of asymptomatic bacteriuria during pregnancy decreases the risk of subsequent pyelonephritis from 20%–35% to 1%–4%.[20] Antibiotic treatment compared to placebo or no treatment was effective in clearing asymptomatic bacteriuria. The incidence of pyelonephritis was reduced. Antibiotic treatment was also associated with a reduction in the incidence of low birth-weight babies but a difference in preterm delivery was not seen.[21]

E. coli, originating from fecal floras that colonize the periurethral area (ascending infection), is the most

common cause of UTI in pregnancy, accounting for 80-90% of cases. Klebsiella, Enterobacter, and Proteus species cause most of the remaining cases. Gram-positive organisms, particularly Enterococcus faecalis and group B Streptococcus (GBS, or S. agalactiae), are also clinically important pathogens.

Pregnant women should be screened for bacteriuria by urine culture at least once in early pregnancy, and they should be treated with 3-7 days of antibiotics if the results are positive. Periodic screening for recurrent bacteriuria should be undertaken following therapy.[7]

An antibiotic with a low adverse effect profile for 7 days is advocated. Beta-lactam antibiotics penicillins, cephalosporins, and nitrofurantoin theoretically can be used safely. There have been few human studies using fosfomycin for the treatment of asymptomatic bacteriuria during pregnancy. TMP-SMX is to be avoided in the first and third trimesters. Fluoroquinolones are contraindicated in pregnancy. Urine culture is done 2 weeks later to document eradication even if clinically responding.

RECURRENT UTIS AND PROPHYLACTIC ANTIBIOTIC

A recurrent UTI can be classified as either a re-infection or a relapse. As infecting pathogens frequently persist in the rectum, it is difficult to clinically distinguish between a relapse and re-infection if the infecting strain is the same.

Prophylaxis has been advocated for women who experience two or more symptomatic UTIs within six months,[22] or three or more over 12 months.[23] A meta-analysis from the Cochrane database evaluated 10 trials involving 430 healthy non-pregnant women with two to three or more UTIs during the previous twelve month period showed that continuous antibiotic prophylaxis for 6-12 months reduced the rate of UTI during prophylaxis when compared to placebo. After prophylaxis two studies showed no difference between groups. However there were more adverse events in the antibiotic group.[24]

Postcoital prophylaxis may be attractive to women who describe a clear relation between sexual intercourse and subsequent lower UTIs. The reduction in the frequency of recurrences when nitrofurantoin, TMP-SMX, or a fluoroquinolone is used after intercourse has approximated that obtained with continuous prophylaxis, although there is no data available from head-to-head comparison trials.

Postcoital TMP-SMX is a safe, effective, and inexpensive approach to the management of recurrent urinary tract infections in young women with both low (two or fewer times per week) and high (three or more times per week) intercourse frequencies. In the only placebo-controlled trial, the infection rate was lower in patients receiving postcoital TMP-SMX (40 mg/200 mg) compared to placebo (0.3 versus 3.6 per patient-year).[25]

Sexual intercourse, diaphragm-spermicide use, and a history of recurrent UTI are strong and independent risk factors for UTI.[2] Women with recurrent UTIs who are sexually active or who use spermicides (particularly in conjunction with diaphragms) should be counseled about the possible association between their infections and sexual intercourse and use of spermicides. Abstinence or a decrease or elimination of the usage of spermicide-containing products may reduce the risk of UTI. Also, it is reasonable to suggest to women that early postcoital voiding and more liberal fluid intake to increase the frequency of micturition might be helpful. Although they have not been shown in controlled studies to be associated with a reduced risk of recurrent UTI, they are unlikely to be harmful. Urologic evaluation is not routinely indicated.

ADJUNCTIVE AND COMPLEMENTARY THERAPY

Phenazopyridine

Phenazopyridine is a urinary tract analgesic, and is ineffective in actual eradication of true UTI pathogens. For treatment of UTI, symptoms will often resolve within 24-48 hours after starting an antibiotic. Patients with severe dysuria or delayed response to antibiotic may receive phenazopyridine for 1-2 days. It is of note that false positive nitrite tests can occur with substances that turn the urine red including phenazopyridine.

Cranberry

Preliminary studies show that cranberry (Vaccinium macrocarpon) juice may be useful to prevent and treat UTIs by inhibiting bacterial adherence to the bladder epithelium. Two Cochrane reviews studied cranberries in treatment and prophylaxis of urinary tract infection. There was no randomized controlled trial that assessed the effectiveness of cranberry juice for the treatment of UTIs.[26] There is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly for women with recurrent UTIs. However its effectiveness for other groups is less certain. The large number of dropouts/ withdrawals indicates that cranberry juice may not be acceptable over long periods of time. It is not clear what is the optimum dosage or method of administration (e.g. juice, tablets or capsules).[27]

EMPIRICAL TREATMENT FOR UPPER UTIS

Upper UTIs deserve more vigorous investigation and treatment due to the possibility of urosepsis. Urine culture with optional blood culture should be taken and the need of hospitalization should be assessed. Patient can be either treated with an oral antibiotic in out-patient setting, or patient should be hospitalized and treated with an intravenous antibiotic depending on severity of symptoms and compliance issue.

For young non-pregnant women with normal urinary tracts presenting with an episode of acute pyelonephritis, 14 days of antimicrobial therapy is appropriate; courses of highly active agents as short as 7 days may be sufficient for mild or moderate cases. Mild cases can be managed with oral antibiotics. An oral fluoroquinolone is recommended or, if the organism is known to be susceptible, TMP-SMX can be considered. If a gram-positive bacterium is the likely causative organism, amoxicillin or amoxicillin/ clavulanic acid may be used alone.[9]

Patients with more severe cases of acute pyelonephritis should be admitted to hospital and treated with a parenteral fluoroquinolone, an aminoglycoside with or without ampicillin, or an extended-spectrum cephalosporin with or without an aminoglycoside; if gram-positive cocci are causative, treatment with ampicillin/sulbactam with or without an aminoglycoside is recommended.[9]

With improvement, the patient's regimen can be changed to an oral antimicrobial to which the organism is susceptible to complete the course of therapy.

Treatment for acute upper UTIs			
Drug	**Usual adult dosage**	**Comment**	**Recommendation rating**
Beta-lactam antibiotics			
Amoxicillin clavulanate	Acute uncomplicated pyelonephritis: 875 mg every 12 hours or 500 mg every 8 hours. Mild to moderate infections One 375-mg tab tds or 625-mg tab bd. Severe infections Two 375-mg tab tds or one 1-g tab bd. 1.2 g every 8 hours, may be increased to every 6 hours for more serious infections.	Active against gram-positive organisms including enterococci. Addition of beta-lactamase inhibitor extends the spectrum of activity to methicillin-sensitive S. aureus as well as anerobes including B. fragilis.	B, III
Ampicillin	IV: 1-2 g every 6 hours.		
Ampicillin-sulbactam	Oral: 375-750 mg bd. IM/IV: 1.5-12 g/day in divided doses every 6-8 hours up to a max daily dosage of 4 g sulbactam.		
Cefotaxime	IV: 1-2 g every 12 hours.	Cephalosporins with extended-spectrum activity. Ceftazidime is active against Pseudomonas while cefotaxime and ceftriaxone are not. Cephalosporins are not active against enterococci.	B, III
Ceftriaxone	IM/IV: 1-2 g every 12-24 hours.		
Ceftazidime	IM/IV: 250-500mg IV or IM every 8-12 hours.		
Cefuroxime	IM/IV: 750 mg every 8 hours		
Aminoglycosides			
Amikacin	IM/IV: 15 mg/kg/day in 2-3 divided doses. Max 1.5 g/day	Possess antipseudomonal activity. Amikacin generally is reserved for multiresistant bacteria.	B, III
Gentamicin	IM/IV: 3-5mg/kg/day in divided doses every 8 hours, or 4-7mg/kg every 24 hours.		
Sulfonamides and trimethoprim			
Trimethoprim - sulfamethoxazole	Oral: 960mg every 12 hours for 7-14 days.	As empirical outpatient treatment.	Uncomplicated: B,II
Fluoroquinolones			
Levofloxacin	Oral, IV: 250 mg every 24 hours for 10 days.	As empirical treatment. For both outpatient and inpatient treatment. Due to activity against gram-positive Streptococci by some fluoroquinolones, extensive use may lead to resistance. Active against Pseudomonas.	Uncomplicated: A, II Complicated: B, III
Ciprofloxacin	Oral: 500 mg every 12 hours for 7-14 days. I.V.: 400 mg every 12 hours for 7-14 days.		
Norfloxacin	Oral: 400 mg twice daily for 10-21 days.		
Ofloxacin	Oral: Complicated: 200 mg every 12 hours for 10 days. 300-600 mg daily in 2-3 divided doses.		

OTHER UTIS

UTI in males

The normal male urinary tract has many natural defenses to infection, including the separation of the urethral opening and the anus, the long urethra as barrier between the urinary bladder and the perineum. Because of these defenses, many experts consider UTIs in males to be complicated, and infections are more likely to be associated with anatomic abnormalities, requiring surgical intervention to prevent sequelae.

For UTI in males without features of acute pyelonephritis or prostatitis, urine culture should be obtained and 10- to 14-day antibiotic therapy is then instituted. TMP-SMX or a fluoroquinolone is preferred. If acute pyelonephritis or prostatitis is suspected, patient should be hospitalized and IV antibiotics should be initiated.

If clinical cure cannot be achieved after antibiotic therapy, a repeat urine culture plus urologic evaluation should be done, and a prolonged antibiotic therapy of 6 weeks as treatment of prostatitis should be considered. TMP-SMX or a fluoroquinolone is a preferred agent for prostatitis caused by gram-negative organisms. If urine culture shows gram-positive organisms, amoxicillin or amoxicillin-clavulanate can be used. The duration of antibiotic treatment for acute prostatitis is 4 weeks to prevent development of chronic prostatitis. For chronic prostatitis 4 to 12 weeks of antibiotics is required.

UTI in pediatrics

E. coli is the most common bacterial cause of pediatric UTI, accounting for approximately 80% of UTI in children. Other gram-negative pathogens include Klebsiella, Proteus, Enterobacter, and Citrobacter. Gram-positive pathogens include *S. saprophyticus*, Enterococcus, and, rarely, *S. aureus.*

The presence of UTI should be considered in infants and young children 2 months to 2 years of age with unexplained fever. Diagnosis of UTI is based on the culture of a properly collected specimen of urine; urinalysis can only suggest the diagnosis.

The usual choices for treatment of UTI orally include amoxicillin, a sulfonamide-containing antimicrobial (TMP-SMX) or a cephalosporin. Emerging resistance of *E. coli* to ampicillin appears to have rendered ampicillin and amoxicillin less effective than alternative agents. Studies comparing amoxicillin with TMP-SMX have demonstrated consistently higher cure rates with TMP-SMX, regardless of the duration of therapy. Agents that do not achieve therapeutic blood concentrations, such as nalidixic acid or nitrofurantoin, should not be used to treat UTI in febrile infants and young children in whom renal involvement is likely.

Infants and young children 2 months to 2 years of age, including those whose treatment initially was administered parenterally, should complete a 7- to 14-day antimicrobial course orally. After a 7- to 14-day course of antimicrobial therapy and sterilization of the urine, they should receive antimicrobials (TMP-SMX, trimethoprim, nitrofurantoin, nalidixic acid) in therapeutic or prophylactic dosages until the imaging studies of the urinary tract are completed.[28] On the other hand, NICE Guidance does not recommend prophylactic antibiotics in infants and children following first time UTI. It may be considered in infants and children with recurrent UTIs.[29] Apart from children with recurrent UTIs, it is reasonable to give antibiotic prophylaxis

to, significant urinary tract anomalies, or significant kidney damage. General advice should be provided on preventing UTIs, such as maintaining adequate fluid intake and avoiding a delay in voiding.

Catheter-associated UTIs

Catheter-associated UTIs (CA-UTI) in patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization is defined by the presence of symptoms or signs compatible with UTI with no other identified source of infection along with not less than 1,000 CFU/ml of not less than 1 bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hours.

In short-term catheterization, *E. coli* is the most frequent species isolated, occurring in around one-third of isolates. Other bacteria isolated include Klebsiella species, Serratia species, Citrobacter species, and Enterobacter species, nonfermenters such as *P. aeruginosa,* and gram-positive cocci, including coagulase-negative staphylococci and Enterococcus species. Funguria, mostly candiduria, is reported in 3%–32% of patients catheterized for short periods of time. On the other hand, UTIs in patients with long-term catheterization are usually polymicrobial. In addition to the pathogens isolated from patients with short-term catheterization, species such as *P. mirabilis, Morganella morganii*, and *P. stuartii* are common.[30]

Seven days is the recommended duration of antimicrobial treatment for patients with CA-UTI who have prompt resolution of symptoms, and 10–14 days of treatment is recommended for those with a delayed response, regardless of whether the patient remains catheterized or not. Specifically, a 5-day regimen of levofloxacin may be considered in patients with CA-UTI who are not severely ill. A 3-day antimicrobial regimen may be considered for women aged not more than 65 years who develop CA-UTI without upper urinary tract symptoms after an indwelling catheter has been removed.[31]

SUMMARY

Treatment of UTI depends on various factors, e.g. patient populations, comorbidity, clinical features, risk factors and diagnosis. Antimicrobial treatment should also tailor for individual patient factors, local antimicrobial resistance surveillance data, and susceptibility testing of bacteria of urine cultures. Due to increasing resistance of UTI pathogens towards TMP-SMX and other antimicrobials, it is not surprising to see some less frequently used antimicrobials to emerge as possible alternatives. We anticipate that specific management of UTIs in region with high resistance rates will be addressed in the upcoming update to IDSA Guidelines for Antimicrobial Treatment of Uncomplicated Acute Bacterial Cystitis and Acute Pyelonephritis in Women which is published in 1999, which is expected to be available in Winter 2011.

Author's background

LAI, Oi-Lun Ellen *graduated from the School of Pharmacy of the Chinese University of Hong Kong. She is currently a pharmacist working in Queen Mary Hospital. Her corresponding e-mail address is lol186@ha.org.hk.*

References

1. Foxman, B. (2002). Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med, 113 Suppl 1A:5S-13S.
2. Hooton TM, et al. (1996). A prospective study of risk factors for symptomatic urinary tract infection in young women. N Engl J Med, 335(7):468-74.
3. Echols, RM, Tosiello, RL, Haverstock, DC, Tice, AD. (1999). Demographic, clinical, and treatment parameters influencing the outcome of acute cystitis. Clin Infect Dis, 29:113.
4. Bent S, et al. (2002). Does This Woman Have an Acute Uncomplicated Urinary Tract Infection? JAMA, 287:2701-10.
5. Stamm WE, et al. (1982). Diagnosis of coliform infection in acutely dysuric women. N Engl J Med, 307(8):463-8.
6. Wilson ML, et al. (2004). Laboratory diagnosis of urinary tract infections in adult patients. Clin Infect Dis., 38(8):1150-8.
7. Nicolle LE, et al. (2005). Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis., 40(5):643-54.
8. Stamm WE, et al. (1980). Causes of the acute urethral syndrome in women. N Engl J Med, 303:409.
9. Warren, JW, Abrutyn, E, Hebel, JR, et al. (1999). Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Clin Infect Dis, 29:745-59.
10. Gupta, K, Hooton, TM, Roberts, PL, Stamm, WE. (2007). Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. Arch Intern Med, 167:2207.
11. Guay DR. (2001). An update on the role of nitrofurans in the management of urinary tract infections. Drugs, 61:353.
12. Product Information: MONUROL(R) sachet oral solution, fosfomycin tromethamine oral solution. (2007). Zambon Switzerland Ltd, Cadempino, Switzerland.
13. Stamm, WE, et al. (1993). Management of urinary tract infections in adults. N Engl J Med,329:1328.
14. Katchman, EA, et al. (2005). Three-day vs longer duration of antibiotic treatment for cystitis in women: systematic review and meta-analysis. Am J Med, 118:1196.
15. Norrby, SR. (1990). Short-term treatment of uncomplicated lower urinary tract infections in women. Rev Infect Dis, 12:458.
16. Hooton TM, et al. (1995). Randomized comparative trial and cost analysis of 3-day antimicrobial regimens for treatment of acute cystitis in women. JAMA, 273(1):41-5.
17. Hooton, TM, et al. (2005). Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: a randomized trial. JAMA, 293:949.
18. Fihn. N (2003). Eng J Med, 349:259-266.
19. Kincaid-Smith P, Bullen M. (1965). Bacteriuria in pregnancy. Lancet,1:395–9.
20. Smaill F. (2001). Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database Syst Rev, 2:CD000490.
21. Smaill FM, Vazquez JC. (2007). Antibiotics for asymptomatic bacteriuria in pregnancy. Cochrane Database of Systematic Reviews, Issue 2. Art. No.: CD000490. DOI: 10.1002/14651858.CD000490.pub2.
22. Nicolle, LE, Ronald, AR. (1987). Recurrent urinary tract infection in adult women: diagnosis and treatment. Infect Dis Clin North Am, 1:793.
23. Ronald, AR, Conway, B. (1988). An approach to urinary tract infections in ambulatory women. Curr Clin Top Infect Dis, 9:76.
24. Albert, X, Huertas, I, Pereiro I, I, et al. (2004). Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Cochrane Database Syst Rev, 3:CD001209.
25. Stapleton, A, Latham, RH, Johnson, C, Stamm, WE. (1990). Postcoital antimicrobial prophylaxis for recurrent urinary tract infection. A randomized, double-blind, placebo-controlled trial. JAMA, 264:703.
26. Jepson RG, Mihaljevic L, Craig JC. (1998). Cranberries for treating urinary tract infections. Cochrane Database of Systematic Reviews, Issue 4. Art. No.: CD001322. DOI: 10.1002/14651858.CD001322
27. Jepson RG, Craig JC.(2008). Cranberries for preventing urinary tract infections. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD001321. DOI: 10.1002/14651858.CD001321.pub4.
28. American Academy of Pediatrics. (1999). Committee on Quality Improvement Subcommittee on Urinary Tract Infection Practice Parameter: The Diagnosis, Treatment, and Evaluation of the Initial Urinary Tract Infection in Febrile Infants and Young Children. Pediatrics, 103(4):843-52.
29. Urinary tract infection: diagnosis, treatment and long-term management of urinary tract infection in children. (2007). National Institute for Health and Clinical Excellence (NICE Guidance).
30. Nicolle LE. (2005). Catheter-related urinary tract infection. Drugs Aging, 22:627–639.
31. TM Hooton, et al. (2010). Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Inf Dis, 50:625-663.

適美治™
Zmax™
(azithromycin extended release)
for oral suspension

Power of ONE dose

You'll have to find a new use for those extra spoons!

Indication[1]

Zmax™ is indicated for the treatment with mild to moderate infections caused by susceptible pathogens in:

- Acute Bacterial Sinusitis
- Community-acquired Pneumonia
  -In adults and pediatric patients 6 months or older

Dosage[1]

It is recommended that Zmax™ be taken on an empty stomach (at least 1 hr before or 2 hrs following a meal)

Adults	Pediatric patients
A full course therapy in a single 2g oral dose	For pediatric patients 6 months or older
	Zmax™ should be taken as a single dose of 60mg/kg OR 1ml/lb
	Pediatric patients weighting 75lb (34 kg) or more should receive the adult dose (2 g)

ZMAX ABBREVIATED PACKAGE INSERT

1. **TRADE NAME: Zmax**
2. **PRESENTATION:** Each bottle of Zmax contains azithromycin dihydrate equivalent to 2g of azithromycin. After constitution with 60 mL of water, each mL of suspension contains 27 mg of azithromycin. The suspension is a white or off-white color and has a cherry/banana flavor.
3. **INDICATIONS:** Mild to moderate infections caused by susceptible isolates of the designated microorganisms. **a) Acute bacterial sinusitis in adults** due to *Haemophilus influenzae, Moraxella catarrhalis* or *Streptococcus pneumoniae.* **b) Community acquired pneumonia** in adults and pediatric patients six months of age or older due to *Chlamydophila pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae* or *Streptococcus pneumoniae,* in patients appropriate for oral therapy.
4. **DOSAGE: Adults:** Zmax should be taken as a single 2 g dose. Zmax provides a full course of antibacterial therapy in a single oral dose. **Pediatric patients 6 months and older:** Zmax should be taken as a single dose of 60 mg/kg (equivalent to 27 mg/lb) body weight. The Zmax dose in mL is equivalent to the child's weight in lb (1 mL/lb dose), for a body weight of less than 75 lb (34 kg). Pediatric patients weighing 75 lb (34 kg) or more should receive the adult dose (2 g). It is recommended that Zmax be taken on an empty stomach (at least 1 hour before or 2 hours following a meal). Constituted suspension should be consumed within 12 hours.
5. **CONTRAINDICATIONS:** Zmax is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin or any macrolide or ketolide antibiotic.
6. **WARNINGS & PRECAUTIONS:** Serious allergic reactions, including angioedema, anaphylaxis, Stevens Johnson syndrome and toxic epidermal necrolysis reported rarely in patients on azithromycin therapy using other formulations. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. *Clostridium difficile* associated diarrhea (CDAD) must be considered in patients w/ diarrhea following antibiotic use. Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome in patients receiving azithromycin therapy. If a patient vomits between 5 and 60 minutes following administration, alternative therapy should be considered. Caution should be exercised in patients with GFR <10 mL/min, due to a higher incidence of gastrointestinal adverse events. Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes* in treatment with macrolides. Prescribing Zmax in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. Careful monitoring of patients when used digoxin, ergotamine or dihydroergotamine, cyclosporine, hexobarbital and phenytoin concomitantly with azithromycin.
7. **INTERACTIONS:** Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants (e.g. warfarin) concomitantly. Azithromycin had minimal effect on the pharmacokinetics of atorvastatin, carbamazepine, cetirizine, didanosine, efavirenz, fluconazole, indinavir, midazolam, sildenafil, theophylline (intravenous and oral), triazolam, trimethoprim/sulfamethoxazole or zidovudine. Co-administration of nelfinavir increases azithromycin serum concentration.
8. **PREGNANCY AND LACTATION:** Pregnancy Category B. Teratogenic effects; should only be used during pregnancy if clearly needed. It is not known whether azithromycin is excreted in human milk, caution should be exercised when administered to a nursing woman.
9. **SIDE EFFECTS: Adults:** Common side effects included diarrhea/loose stools, nausea, abdominal pain, headache, vomiting. Less common side effects included palpitation and arrhythmias including ventricular tachycardia and hypotension, chest pain, constipation, dyspepsia, flatulence, gastritis, oral moniliasis, vaginitis, dizziness, vertigo, asthenia, rash, pruritus, urticaria, taste perversion. **Pediatric Patients in clinical trials:** Common side effects included vomiting, diarrhea, loose stools, abdominal pain, nausea, rash, dermatitis, anorexia, fever. Less common side effects included chills, flu syndrome, headache, abnormal stools, constipation, dyspepsia, flatulence, gastritis, gastrointestinal disorder, hepatitis, leucopenia, agitation, emotional liability, hostility, hyperkinesia, insomnia, irritability, parasthesia, somnolence, asthma, bronchitis, cough increased, dyspnea, pharyngitis, rhinitis, fungal dermatitis, maculopapular rash, pruritus, urticaria, otitis media, taste perversion, dysuria.

• Reference: HKPI (version date September 2010) • Date of preparation: Oct 2010 • Identifier number: AZIT1010

Reference: 1. Zmax™ Hong Kong package insert. Sep 2010.

Full prescribing information is available upon request.
Please review full product information before prescribing.

Pfizer Corporation Hong Kong Limited
16/F., Stanhope House, 738 King's Road, North Point, Hong Kong
Tel: (852) 2811 9711 Fax: (852) 2579 0599
Website: www.pfizer.com.hk

ZMA11002P

CONDOR

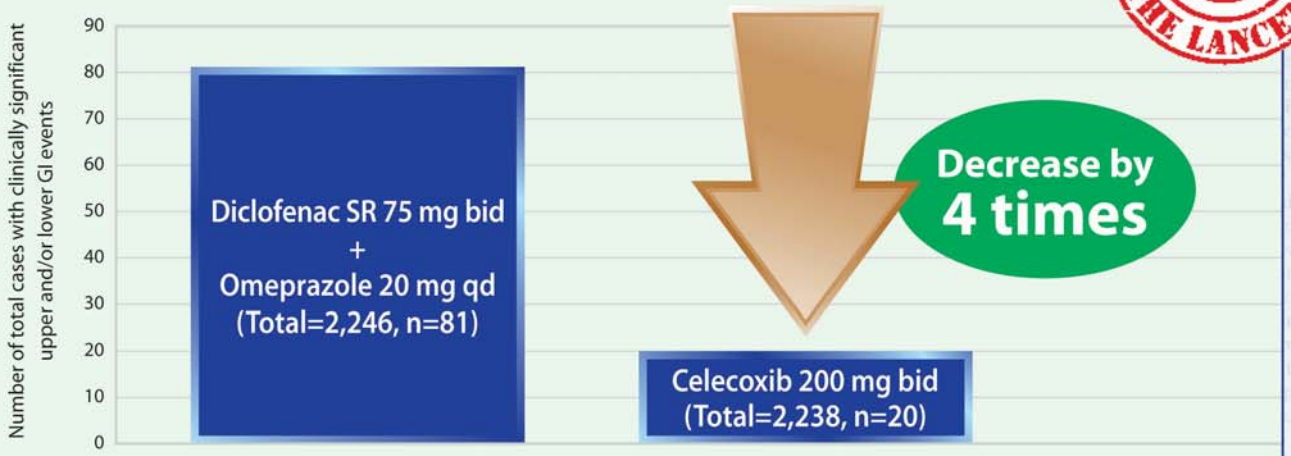
Celecoxib versus **O**meprazole a**N**d **D**iclofenac
in patients with **O**steoarthritis and **R**heumatoid arthritis

Celecoxib vs. Diclofenac + Omeprazole:

Patients treated with Celecoxib had a **LOWER RISK** of Clinically Significant Upper and/or Lower GI Events[1]

CONDOR NEW STUDY THE LANCET

Patients with adjudicated clinically significant upper and/or lower GI events



Hazard ratio was 4.3 in favour of Celecoxib, *P<0.0001*

- Proven efficacy in various pain models[2-5]
- The Only FDA-approved COX-2 inhibitor[6]
- Option for millions of patients for over 10 straight years[7]

Strengthening confidence across Asia FOR OVER 10 YEARS

CELEBREX®
(CELECOXIB)

Reference: 1. Chan FKL, Lanas A, Scheiman J, Berger MF, Nguyen H, Goldstein JL. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR) a randomized trial. J Rheumatol. 2010;37:167-174. 2. Graham DY, Chan FK. Gastroenterology 2008;134:1240-1257. 3. Nadarajah A, et al. Singapore Md J 2006; 47:534. 4. Petri M, et al. J Rheumatol 2004;31:1614-20. 5. Cheung R, et al. Clin Ther 2007;29 [Theme Issue]:2498-2510. 6. Food and Drugs Administration (FDA). http://www.fda.gov. Accessed February 10, 2011. 7. About Celebrex 2010. Available at URL http://www.celebrex.com/about-celebrex.aspx. Accessed Feb 10, 2011.

CELEBREX ABBREVIATED PACKAGE INSERT. 1. TRADE NAME: Celebrex. **2. PRESENTATION:** Capsules contain either 100 mg , 200 mg or 400 mg of celecoxib. **3. INDICATIONS: Adult:** For relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, management of acute pain, treatment of primary dysmenorrhea. **4. DOSAGE:** For more dosage information, please refer to the full package insert. **5. CONTRAINDICATIONS:** Hypersensitivity to celecoxib, aspirin or other NSAIDs or demonstrated allergic-type reactions to sulfonamides or experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Use as treatment for perioperative pain in the setting of CABG surgery. **6. WARNINGS & PRECAUTIONS:** Increased risk of serious adverse cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal; Patients with known CV disease or risk factors for CV disease may be at greater risk; Caution in patients with hypertension, fluid retention or heart failure; Can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. Extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding; Special care should be taken as most spontaneous reports of fatal GI events are in elderly and debilitated patients; A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, Celebrex should be discontinued; Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion; Not recommended in these patients with advanced renal disease; Anaphylactoid reactions have occurred in patients without known prior exposure to Celebrex; Should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs; Can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events can occur without warning and in patients without prior known sulfa allergy. Patients should be informed about the signs and symptoms of serious skin manifestations and use of drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity; Cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency; Should not be administered to patients with aspirinsensitive asthma and should be used with caution in patients with preexisting asthma; Has not been shown to reduce the risk of gastrointestinal cancer or the need for prophylactic colectomy or other FAP-related surgeries in FAP. Therefore, the usual care of FAP patients should not be altered; The pharmacological activity in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions; The concomitant use with any dose of a nonaspirin NSAID should be avoided due to the potential for increased risk of adverse reactions. **7. INTERACTIONS:** ACE inhibitors and angiotensin II antagonists, aspirin, fluconazole, furosemide, lithium, NSAIDs, warfarin and drugs that inhibit cytochrome P450 2C9. Potential interaction with drugs that are metabolized by P450 2D6. **8. PREGNANCY AND LACTATION:** Pregnancy Category C; Pregnancy category D from 30 weeks of gestation onward because it may cause premature closure of the ductus arteriosus; Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and should be avoided during the third trimester of pregnancy; Effects on labor and delivery in pregnant women are unknown; Caution should be exercised in nursing women. **9. SIDE EFFECTS:** Abdominal pain; Diarrhea; Dyspepsia; Flatulence; Nausea; Back pain; Peripheral edema; Injury-accidental; Dizziness; Headache; Insomnia; Pharyngitis; Rhinitis; Sinusitis; Upper respiratory infection; Rash. **Reference:** HK PI (Jun 2009). **Date of preparation:** Nov 2010. **FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.**

Pfizer Corporation Hong Kong Limited 16/F., Stanhope House, 738 King's Road, North Point, Hong Kong Tel: (852) 2811 9711 Fax: (852) 2579 0599 Website: www.pfizer.com.hk

CEL11002P

Mini-Review on Neuropsychiatric Properties of the Root Extract of Valerian (*Valeriana officinalis* L., 瓦莱里安)

BAIBADO, Joewel Tarra[a]; CHEUNG, Hon–Yeung[b]*

[a]*Iloilo Doctors' College, College of Sciences & Nursing, 5000 West Ave., Molo, Iloilo City, Philippines*

[b]*Research Group for Bioactive Products, Department of Biology & Chemistry, City University of Hong Kong, Hong Kong SAR, China*

Botanical Names: *Valeriana officinalis* L, *Centranthus ruber, Valeriana angustifolia, Valeriana edulis, Valeriana jatamansii, Valeriana officinalis, Valeriana psuedofficinalis, Valeriana sitchensis, Valeriana wallichii,*

Family: Valerianaceae

Latin: derived from Valerius, Radix **Valerianae**

Common names/other names: Garden valerian, Garden heliotrope, valerian, all-heal, amantilla, carpon's tail, heliotrope, setewale, setwall, vandal root, valerian root, St. George's herb, Baldrian, Baldrianwurzel, Belgium Valerian, Common Valerian, Fragrant Valerian, Indian Valerian, Mexican Valerian, Pacific Valerian, Tagar, Tagar-Ganthoda, Tagara, Valeriana, Valerianae radix, Valériane, Valériane Officinale, Valeriana rhizome.

Chinese Name: chih ts'ao; 瓦莱里安

Part Usually Used: root

Common Uses: occasional sleeplessness, occasional nervousness, mild to moderate mood swings or a depressed mood caused by everyday stress, nervous tension or anxiety

ABSTRACT

Valerian extract is traditionally used to relieve muscle spasms, to treat insomnia, hysteria, nervous tension, fatigue and menstrual cramps. It is among the most popular sleeping aids in Europe. Chemical analysis and clinical experiments confirm the sedative compounds present mainly in the alcoholic extracts made from the fresh roots of *Valeriana officinalis*. Scientific studies on the effects of the active chemical components reveal that moderate doses of valerenic acid, valepotriates and other flavonoids derived from the valerian root promote relaxation of the Central Nervous System (CNS) to reduce overactive behaviors that include occasional nervousness, nervous tension, and anxiety and panic attacks. However, the exact nature and mechanism of action remain unknown.

Keywords: *Valerian, sedative, spasmolytic, valepotriates, anxiolytic, insomnia*

INTRODUCTION

Valerian has been used as a medicinal herb since ancient Greek and Roman times. Its properties were described by Hippocrates and it was prescribed by Galen as remedy for insomnia. It was sometimes placed in the wedding clothes of the groom to ward off the "envy" of the elves in medieval Sweden. Valerian can be consumed as a tea.[1] This plant has sweet-smelling pink or white flowers. The name "Valerian" in Latin means "to be strong or healthy", and this can be attributed to its medicinal use. It may also refer to its strong odor.[2]

Ancient Greeks used the plant in a variety of medical disorders ranging from digestive ailments, urinary tract disorders, liver problems, nausea and insomnia. For centuries, it has been traditionally used as a diuretic and also used for hysteria, sleeplessness, epilepsy and nervousness.[2]

In Germany, it was used for unruly children while German women used it as a perfume in the 16th century, as a condiment in medieval times, and as a coffee substitute.[2] Valerian has often been used for its sedative properties in complementary and alternative medicine. It has been recommended for epilepsy but supporting evidence from modern research is lacking. Currently, the herb is used mainly for insomnia remedy.

TAXONOMY, DISTRIBUTION, AND NOMENCLATURE

Valerian *(Valeriana officinalis* L.*)* is a highly variable species of the Valerian family (Valerianaceae) occurring in Southeastern, East-central, Eastern Europe, extending to the Southern Alps and South Sweden.[3] It is native to Europe, South Africa, and parts of Asia. Valerian was brought to North America by colonists at an early date. It escaped from cultivation, becoming naturalized from Nova Scotia to Pennsylvania, Quebec, and Ohio to Minnesota.[3] The genus *Valeriana* includes upwards of 250 species of the South Africa, the Andes, and northern temperate zone.[4] Twenty species are indigenous to Europe.[5] There are sixteen native or naturalized species, with five subspecies and two varieties in North America (exclusive of Mexico).[5] Linnaeus noted that the plant is named in honor of Roman emperor from 253-260, Publius Aurelius Licinus Valerianus. The name "valerian" is derived from the Latin word "valere" meaning "to be in health".[4] Only four of the 30 species of *Valeriana* distributed in Southwest and Northeast China were used mostly as medicine.[6] The large-scale propagation of the endangered plant offer an attractive alternative for its production for medicinal purposes since the valepotriate production in *in vitro* cultures of *Valeriana edulis* ssp. *procera* was closely related to rhizome and root differentiation in the reproductive stage.[7]

DESCRIPTION AND IDENTIFICATION OF VALERIAN

Macroscopic appearance

The plant grows typically from a short rhizome to 2 m high flowers after autumn establishment and winter dormancy, following death in winter. Valerian (Fig. 1) bears many small white or pink fragrant flowers in a dense head of several stalked clusters and has pinnately-divided leaves with six to 10 pairs of

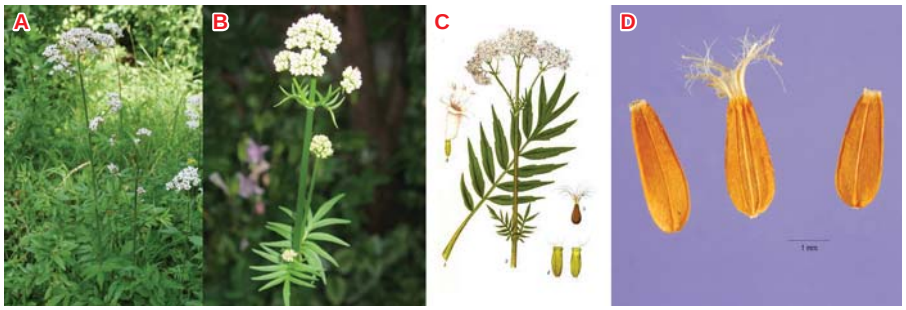


Figure 1. *Valeriana officinalis L. (From L to R: (A) V. officinalis in its habitat; (B.) a close up view of individual stem with flowers and leaves; (C) a scratch diagram of flowers, leaves and seeds and (D) seeds at magnified scale. (Photos taken from http/www.alibaba.com, Carl Lindman's Bilder ur Nordens Flora, and by Michael Moore)*

lance-shaped leaflets. These heads bear small (5 mm) tapered seeds that are spread by wind. The fresh root has a very distinctive and strong penetrating odour and appears like a mop - a mass of long, white, relatively unbranched roots, up to 5 mm in diameter and 30 cm long. The plant is highly variable. There are diploid, tetraploid, and octaploid types. Polyploidy occurs in V. *officinalis*. Central European valerian is usually tetraploid and English valerian is usually octaploid.[8]

The plant has obovoid, short rhizome with numerous fine and long dark to grayish brown roots (Fig 2). The roots are usually brittle with 10-15 cm in length, 0.1-0.3 cm in diameter and with fine longitudinal wrinkles. The rhizome is 1-2 cm in length. The diameter with buds and stem at the crown remains the same. It has hard texture and difficult to break. Its stolons have thick long and extremely small scaly leaves. It has a somewhat sweet and slightly spicy, bitter taste. Its strong odor resembles camphor and valeric acid. The rhizome is pale to grayish brown, obconical to cylindrical shape up to 50 mm in diameter and long. The base is elongated or compressed with numerous roots emerging to it. The apex has a cup shaped scar with rare stem bases. The pith exhibits a central cavity traversed with septa. The roots are cylindrical and numerous, 1-3 mm in diameter and sometimes more than 100 mm long. A few filiform fragile secondary roots are present. It has short fibrous fractures. The stolons appear yellowish-gray showing prominent nodes separated with longitudinally striated internodes each 20-50 mm long.[9-10]

Microscopic description

The transverse section of the root (Fig. 2) reveals the suberized epidermis, phloem fibers, a grayish brown stele and a thick, light grayish brown cortical layer. The exodermis is made up of suberized cells containing essential oil droplets. Parenchyma cells containing starch are also evident. Yellow stone cells are also evident.[9] The outer suberized collenchymatous cortex contains resins. The inner cortex is made up of polygonal to round cells filled with both simple and compound starch. The endodermis is made up of suberized, tangentially elongated cells. The pericycle is starch filled and continuous. It has indistinct cambium. The phloem zone is surrounded with parenchyma. Starch filled cells also surround the vascular bundle forming an interrupted ring. The rhizome has numerous vascular bundles coming from the roots and stolons. The epidermis and exodermis are partly replaced with poorly developed periderm. The central pith has numerous cavities of various sizes separated with sclerified plates. The powder is light brown with numerous fragments of parenchyma cells filled with starch granules. There are also cells with light brown resins, rectangular sclereids with pitted walls, isolated xylem in non-compact bundles, some cork cells and absorbing root hair fragments present.[10]

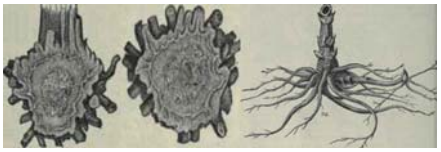


Figure 2. *V. officinalis root (L to R:(A) longitinual-section, (B)cross-section, and (C) rhizome)*[11]

BIOACTIVE CONSTITUENTS

a) Monoterpenes (Bornyl acetate; valepotriates) and sesquiterpenes (valerenic acid, valerenol)

Monoterpenes and sesquiterpenes are compounds found in valerian. Both are known to have sedative effects except that the former is cytotoxic and the latter has no such effect. Sesquiterpenes showed a good and significant effect to improve poor sleep without side effects being observed.[12] These compounds include bornyl acetate (MF:$C_{12}H_{20}O_2$; MW:196.286) and the major constituent of valerian which is valerenic acid (MF:$C_{15}H_{22}O_2$; MW:234.33; Fig. 3).[13] Both valerenic acid and valerenol enhanced the response to GABA at multiple types of recombinant GABA(A) receptors.[14] The relationship between the content of sesquiterpenic acids (valerenic acid, acetoxyvalerenic acid) and the modulation of GABA(A) receptors by Valerian extracts of different polarity has been investigated.[15] Valerenic acid was also found out to stimulate chloride currents through GABA(A) receptors.[16] It is also a partial agonists of the 5-HT(5a) receptor.[17] (-)-borneol and (+)-Borneol, a bicyclic monoterpene from essential oils of valerian, has a positive modulating action at GABA(A) receptors, and at high concentrations (>1.5mM) (+) directly activated GABA(A) receptors producing 84% and 89%, respectively, of the maximal GABA response.[18] Sesquiterpenes and iridoids were studied for their metabolic changes upon incubation with freshly prepared rat hepatocytes and subsequently analysed phytochemically as well as pharmacologically *in vitro*.[19]

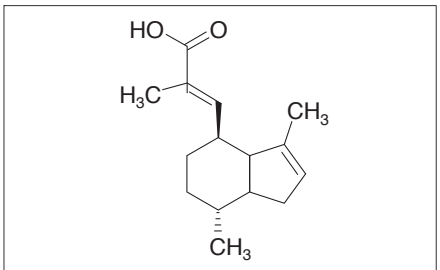


Figure3. *Structure of valerenic acid*[20][21]

b) Lignan (hydroxypinoresinol)

This compound has the ability to bind to benzodiazepine receptors.[13]

c) Linarin (flavone)

A flavone glycoside, linarin, which attribute to the sedative and sleep-enhancing properties, has been identified in *Valeriana officinalis*.[22]

d) Hesperidin

Another reported component that produces sedative and sleep-enhancing properties of valerian is due to 2S(-)-hesperidin.[23]

e) Methylapigenin

6-methylapigenin from *Valeriana wallichii*, was able to potentiate the sleep-enhancing properties of hesperidin and was found to have anxiolytic properties as well.[23] In the crude drug, the calculated percentage of 6-methylapigenin was in the range of 0.013% to 0.0013%.[24]

f) Valtrate

Valtrate, a Rev-transport inhibitor from the nucleus to cytoplasm was isolated from *Valerianae radix*.[25]

IDENTIFICATION, ISOLATION, AND PURIFICATION OF BIOACTIVE COMPONENTS

To differentiate *Valeriana procera* Kunth from *V. officinalis* L. and other commercially important Valerian species such as *V. jatamansi* Jones, *V. edulis* Nutt, and *V. sitchensis* Bong, macro- and microscopic comparative analyses were performed by Joshi *et al*. (2005).[26] Investigation for the terpenoid compositions by means of GC and GC/MS analyses of the essential oils, as well as by one- and two-dimensional NMR studies of the isolates were performed so as to determine the chemical diversity of 4 *Valeriana* genera, including *V. wallichii*.[27] Clionasterol-3-O-beta-D-glucopyranoside and a mixture of 6'-O-acyl-beta-D-glucosyl-clionasterols have been isolated from the chloroform extract of *Valeriana officinalis*. GC-MS analysis was used to identify the acyl moieties.[28]

To establish the fingerprint of the hydrophilic constituents of *Valeriana* medicinal plants, the HPLC-UV assay was done.[29] For stability control, a HPLC-method for separation of medium polar and nonpolar compounds in preparations of *Valeriana officinalis* was established. As degradation products in Valerian root, hydroxyvalerenic acid, pinoresinol & hydroxypinoresinol were identified.[30]

Structures of two new lignans along with 5 known compounds have been isolated from the roots of *V. prionophylla* and have been established on the basis of 1D and 2D NMR experiments. They were found to have a powerful antioxidative and vasorelaxant activities.[31] In the enantioselective total synthesis of valerianannoids A-C from (R)-carvone, a tandem intermolecular Michael addition-intramolecular Michael addition-alkylation sequence and an electron-transfer-mediated 6-endo-trig cyclization as key steps were employed.[32]

Structures of two new flavone glycosides, including acacetin 7-O-beta-sophoroside, have been isolated from the rhizomes and roots of *V. jatamansi* together with 15 known compounds were determined by spectroscopic and chemical means.[33]

The interspecific and intraspecific comparison of valepotriates contents in three *Valeriana* plants, *V. jatamansi* Jones, *V. officinalis* L., and *V. officinalis var*. *latifolia* Miq. shows that they are different. Among them, *V. jatamansi* Jones has the highest valepotriate content.[34] Spectroscopic data were used to elucidate the structure of a new isolated bicyclic sesquiterpene acid, (-)-3 beta,4 beta-epoxyvalerenic acid together with valerenic acid and hexadecanoic acid.[35] Reversed-phase HPLC was employed to quantitatively estimate the valtrate, DIA-valtrate, acevaltrate, 1-beta-acevaltrate and didrovaltrate in the leaves, flowers, stems and roots of 9 Valeriana species including *V. glechomifolia* which was the richest one for valepotriates.[36] Spectroscopic data interpretation were used to elucidate the structures of 5 new iridoids, including 1-homoacevaltrate,1-homoisoacevaltrate along with 10 known analogues, which were isolated from the rhizomes and roots of *V. jatamansi*.[37-38] UV, NMR and mass spectral data were used to identify the flavonoid 6-methylapigenin isolated from the rhizomes and roots of *V. wallichii*.[24] Capillary electrophoresis method, with a detection limit of 5.8 micrograms/ml or less was developed by Mikell *et al.* (2001) to determine sesquiterpenes like valerenic acid, its hydroxy and acetoxy derivatives.[39]

Ultrasonically assisted extraction was performed in experiments related to the industrial production of medicinal tinctures of sage and valerian (*Valeriana officinalis* L.) and High Performance Liquid Chromatography (HPLC) was used to examine the influence of ultrasound on the quality of valerian tincture.[40] To evaluate the recoveries of some characteristic components with different polarities and structures present in the headspace of four aromatic medicinal plants including *V. officinalis*, the performance of 8 commercially available solid-phase microextraction fibres was compared by Bicchi *et al*. (2000).[41] Different species of Valeriana yielded 11.65-0.05 mg/g of Valerianic acid derivatives (VAD) and 1.81-0.03 mg/g of valepotriates using HPLC analysis and the variation between individuals of one cultivar of *V. officinalis* ranged from 12.34 to 3.01 mg/g of VAD and 3.67-0.92 mg/g of valepotriates.[42] Structure elucidation of tamariscene, a new sesquiterpene, valerena-4,7(11)-diene and five new pacifigorgiadienes from the essential oil of *Valeriana officinalis*, was carried out by NMR spectroscopy and chemical correlations.[43]

It was found out by Cavadas *et al.* (1995) that water and alcoholic extracts, containing amino acids and valerenic acid, displace 3H-muscimol from synapse membrane of rat brain.[44] Spiking experiments with inactive extract and profiling active extracts such as valerian extract containing known GABA (A) receptor ligand valerenic acid were used to validate the protocols for an approach for rapid HPLC-based profiling for new GABA (A) ligands of natural origin.[45] Hydrodistillation and supercritical CO_2 were used to identify forty-seven components representing 89.3% and 35 constituents varying from 86.1% to 95.1% of the essential oil extracted from *V. officinalis* L. roots growing wild in Iran.[46] Various spectral analysis and chemical conversion were used to isolate and identify the 4 compounds including valerenic acid, beta-sitosterol, and ursolic acid from *V. officinalis* L.[47] On the basis of chemical reactions and extensive NMR data, epoxysesquithujene, a new sesquiterpene epoxide has been characterized in the essential oil of *V. hardwickii var. hardwickii*.[48] Pobozniak (2007) observed the species composition of thrips from flowers of *V. officinalis* L., *Hypericum perforatum* L. and *Levisticum officinale* and the periods of the occurrence of the particular species of thrips and their numerousness.[49] Bioassay-guided fractionation of crude extracts of the aerial parts of *V. sorbifolia* isolated 4 new diene valepotriates, sorbifolivaltrates A-D, and the known compounds isovaltrate, valtrate, seneciovaltrate, valtrate hydrine B3, and valtrate hydrine B7.[50]

Metal content of valerian root using atomic spectrometry was determined and found out to be below toxic level as studied by Grippo *et al.* (2006).[51-52] From the roots of *V. fauriei*, three novel three-membered ring sesquiterpenoids, named kissoone A, kissoone B, and its acetylated product, kissoone C, were isolated and their structures were elucidated on the basis of spectroscopic analysis.[53] In addition, a new iridoid glycoside, 10-isovaleryl kanokoside C, and a new sesquiterpene, together with two known compounds were also isolated.[54,55]

Navarrete *et al.* (2006) performed analysis of chlorogenic acid, lignans, flavonoids, valerenic acids, and valpotrates in various valerian samples using liquid chromatography.[56] Slanc *et al.* (2006) identified the constituent drugs of a sedative tea made of Valerianae radix (*Valeriana officinalis* L.), Lupuli strobuli (*Humulus lupulus* L.), Melissae folium (*Melissa officinalis* L.) and Menthae piperitae folium (*Mentha piperita* L.) using restriction analysis of ITS DNA and real-time PCR.[57] A commonly used marker for qualitative & quantitative analysis of valerian root & valerian products was described.[58] The continuous presence of 5.71 microM

indole acetic acid, in micropropagated *V. glechomifolia* culture resulted in the best performance in valepotriate production, growth and survival under *ex vitro* conditions following plant acclimatization.[59] Increased processing temperature favors extraction kinetics, but provokes moderate degradation of valerenic acids in the study of extraction of valerenic acids from dry ground rhizomes of *V. officinalis*.[60] Hydroxyvalerenic and valerenic acid concentrations were assayed by HPLC and a drug release test suitable for studying and comparing different valerian tablets was established.[61-62] Furthermore, it was found out by Torrado (2003) that the uncoated tablet formulation has the fastest release profile.[61]

Water-soluble polysaccharides from the roots of valerian was extracted using ultrasound-assisted extraction.[63] NMR spectroscopy and MS spectrometry represent fast and convenient direct analyses of valerian tinctures.[64] HPLC fingerprints of the antiarrhythmic fraction of *V. officinalis* is simple and accurate with a good reproducibility and provides a reference standard for its quality control.[65] Arbuscular mycorrhizal (AM) symbiosis treatments significantly increased the levels of sesquiterpenic acids in the underground parts of valerian.[66] New germacrane-type sesquiterpenoids, volvalerenals and volvalerenic acids, were isolated from a chloroform extract of the roots of *V. officinalis* var. *latifolia*. Their structures and relative configurations were elucidated on the basis of spectroscopic data interpretation. Their effects on acetylcholinesterase were also evaluated.[67] Del Valle-Mojica *et al.* (2011) investigated the effects of two valerian extracts (aqueous and hydroalcoholic) through [^{3}H]Glutamate ([^{3}H]Glu) and [^{3}H]Fluorowillardine ([^{3}H] FW) receptor binding assays by using rat synaptic membranes in the presence of different receptor ligands (Fig. 4).[68] They also found out that factors such as the extraction solvent and stability of the extracts are critical to determine changes in selectivity for glutamate receptor (GluR) interaction.[68]

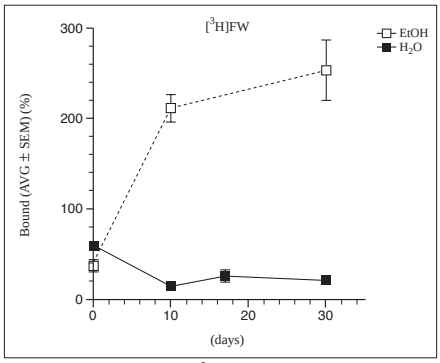


Figure 4. *Changes in ^{3}[H]Fluorowillardine binding with time. Initially, a 60% of inhibition is observed with the aqueous extracts while the hydroalcoholic extract inhibits only a 38%. However, with time, the inhibitory effects of the aqueous extract increase to 85% whereas the hydroalcoholic extract markedly potentiates (200%) ^{3}[H]Fluorowillardine ([^{3}H]FW) binding to AMPA receptors.[68]*

PHARMACOLOGICAL EFFECTS

Alleviation of Sleep problems

Diaper and Hindmarch (2004) found out that valerian at doses 300-600 mg is ineffective as an acute dose for sleep problems.[69] In another study conducted by Dimpfel and suter (2008), found out the superiority of the valerian/ hops combination over placebo. This investigation focuses on the question if a single administration can be an effective sleep aid.[70] Their investigation has shown evidence that a valerian/hops fluid extract can be used successfully using a single administration to treat insomnia.[70-76] Valerian extract LI 156 (Sedonium) 600 mg/die showed a comparable efficacy to 10 mg/die oxazepam in the therapy of non-organic insomnia.[77-78] Donath *et al*. (2000) carefully designed a study to assess the short-term (single dose) and long-term (14 days with multiple dosage) effects of a valerian extract on both objective and subjective sleep parameters. They found out that treatment with the herbal extract demonstrated positive effects on sleep perception and sleep structure of insomnia patients.[79]

They recommended it for the treatment of patients with mild psychophysiological insomnia.[76,79-83] In the appropriate dose , the investigated hop-valerian preparation is a sensible alternative to benzodiazepine for the treatment of nonchronic and non-psychiatric sleep disorders.[84-85] According to Jacobs *et al.* (2005) the herbal extracts kava and valerian are the leading dietary supplements used in the self-management of anxiety and insomnia, respectively.[86-90] However, in the study of Coxeter *et al.* (2003), valerian was not shown to be appreciably better than placebo in promoting sleep or sleep-related factors for any individual patient or for all patients as a group.[91] In the study of Gooneratne (2008) on complementary and alternative medicine for sleep disturbances in older adults, it indicates that valerian has shown a benefit in some, but not all clinical trials.[92-94] Hence, valerian as a treatment for insomnia is inconclusive.[95-96]

According to Francis *et al.* (2002), there is evidence to suggest that valerian may be useful in the safe and effective long-term treatment of intransigent sleep difficulties in children with intellectual deficit.[97] In another study of Poyares *et al.* (2002), also suggested that valerian had a positive effect on withdrawal from benzodiazepines(BDZ) use.[98-99] Valerian was found out to improve subjective experiences of sleep when taken nightly over one- to two-week periods and it appears to be a safe sedative/hypnotic choice in patients with mild to moderate insomnia.[100-104] Leathwood *et al.* (1982) found that there was a significant decrease in sleep latency with dosages of 450 mg of valerian compared to placebo. No further improvement in sleep latency upon doubling the dose.[80] The associations between melatonin use and insomnia and between valerian use and insomnia were analyzed by Bliwise and Ansari (2007).[105-107] Valerian extracts produced beneficial effects on sleep architecture by diminishing the time of stages 1 & 2 in non-REM sleep while increasing delta sleep.[108-109] In a randomised, double-blind, clinical, comparative study showed no differences in the efficacy for valerian and oxazepam and more favourable adverse effect profile of valerian among non-organic & non-psychiatric insomniacs was also reported.[110] Medicinal baths with added pine oil or valerian improve well-being and sleep among fibromyalgia patients.[111] It is also a good sleep aid among patients with rheumatoid arthritis.[112] The effect of valerian extract preparation (BIM) also showed that the BIM could be useful as a sleep-inducer.[113] Valerian extract may be useful as an herbal medicine having not only sleep-inducing effects but also sleep quality-enhancement effects.[114] Concurrent administration of powdered *Leonurus cardiaca* and valerian root suspensions demonstrated maximum prolongation of barbiturate-induced sleep.[115]

Sedative

The sedative effects of the aromatherapeutical use of commercial valerian root oil (Chinese origin) and of pure fragrance compounds: borneol, isoborneol, bornyl acetate (main constituent of the valerian root oil) and isobornyl acetate was investigated in an animal experiment (mice).[116] Monoterpene bornyl acetate has been shown to have a direct action on the amygdaloid body of the brain and valerenic acid has been shown to inhibit enzyme-induced breakdown of GABA in the brain resulting in sedation. Although the mode of action is not clearly known, valepotriates contribute to the overall activity by possessing sedative activity on the CNS. They act

as prodrugs which are transformed into homobaldrinal which has been shown to reduce the spontaneous motility of mice. The aqueous extracts of the roots contain appreciable amounts of GABA which could directly cause sedation but there is some controversy surrounding the bioavailability of this compound as shown in recent studies.[12,117-121]

Another recent finding is its ability to bind to benzodiazepine receptors due to the presence of a lignan, hydroxypinoresinol.[13] Wheatley (2001) claimed that valerian has sedative property without dependence potential or any appreciable side-effects.[122-123] It has been described as acting as a stimulant in fatigue and a sedative in agitated states.[124-126] Ample evidence of the value of valerian as a sedative has provided by long-standing clinical experience. Variations in dosage, as well as quality of commercial preparations are possible reasons for the discrepancies in results.[13,125,127] To produce satisfactory sedative, spasmolytic, and sleep-inducing effects, a whole teaspoonful of tincture is needed.[127] Leathwood *et al*. 1982 noted that one of the most appealing aspects of valerian as a sedative is that it does not leave the user with a "hangover-effect" and it does not interact with alcohol. The authors conducted additional studies, with the ultimate conclusion that the extracts helped to significantly improve sleep quality of those suffering from mild insomnia, with minimal side effects.[80] The affinity and selectivity of two *V. adscendens* extracts (methanolic and aqueous) towards noradrenergic, serotononergic, and dopaminergic receptors by a preliminary binding screen was examined.[128]

Anxiolytic

Andreatini *et al.* (2002) suggested that the valepotriates may have a potential anxiolytic effect on the psychic symptoms of anxiety. However, results must be viewed as preliminary since the number of subjects per group was very small. [129-130] In the study by Miyasaka *et al.* (2006) found out that there is insufficient evidence to draw any conclusion about the efficacy or safety of valerian compared with placebo or diazepam for anxiety disorders.[131] Also, the results of the experiments of Kennedy and Dempster (2006) suggest that a combination of *Melissa officinalis* and *V. officinalis* possesses anxiolytic properties that deserve further investigation.[132] Bhattacharyya *et al.* (2007) showed that *V. wallichii* did not only significantly ($p < 0.001$) attenuate stress and anxiety, but also significantly ($p < 0.001$) improve depression and also enhanced the willingness to adjustment.[133] However, ginkgo and valerian do not appear to be useful in reducing depression or anxiety in perimenopausal and postmenopausal women.[134] Valerian extract is one of the agents recommended to correct psychoemotional state in women with dyshormonal focal breast diseases.[135] The antianxiety effect of valerian and grandaxin fluctuates during daytime wakefulness in humans with different chronotypes.[136] The combination of St John's wort WS 5572 and valerian extract for treating depressive disorders in comorbidity with anxiety disorders was well tolerated, and no side-effects occurred.[137-138] Using mice and rats, evaluation of CNS-related effects of valerian extracts shows not sedative but anxiolytic and antidepressant activity.[139-140] Smaller increases of the heart variables during and after stress evocation transport simulation in pigs supplemented with sedafit, (a commercial herbal product containing *V. officinalis* L. and *Passiflora incarnata* L.), suggested sedative and antianxiety effects.[141]

Mental stress, memory enhancement, alertness, concentration, cognitive and psychomotor effects

Cropley *et al.* (2002) investigated whether valerian could moderate the effects of psychological stress induced under laboratory conditions in a group of healthy volunteers. The results suggest that valerian may be beneficial to health by reducing physiological reactivity during stressful situations.[142] Experimental animals exposed to chronic stress and receiving psychotropic drugs (phenazepam, Atarax, Fluanxol, and valerian) were studied based on their free radical oxidation in the brain and blood serum.[143] Vonderheid *et al.* (2000) showed reproducible pharmacodynamic effects to the Central Nervous System (CNS) and responses to target organs after intake of the high dosage of valerian-hops mixture.[144] Kuhlmann *et al.* (1999) concluded that neither single nor repeated evening administration of 600 mg of valerian root extract (VRE) has a relevant negative impact on reaction time, alertness and concentration the morning after intake.[145]

The effect of an aqueous extract obtained from the roots of *V. officinalis* was investigated by Santos *et al.* (1994) on the uptake and release of GABA in synaptosomes isolated from rat brain cortex. Either in the absence or in the presence of K+ depolarization, the aqueous extract of valerian inhibited the uptake and stimulated the release of [3H] GABA. The release was independent of the presence of Ca^{2+} in the external medium and Na^{+}-dependent. It is concluded that valerian extract releases [3H]GABA by reversal of the GABA carrier, which is Na(+)-dependent and Ca(2+)-independent. This increase in [3H]GABA release appears to be independent from the membrane potential and Na(+)-K(+)-ATPase activity.[146] It was also determined that valerian was statistically superior, and the absence of side effects confirmed its safety and efficacy in the treatment of emotional tension disturbances.[80]

In a study by Arushanian *et al.* (2004) regarding the effect of tofisopam and valerian extract on short-term memory and anxiety states in healthy humans, it was revealed that valerian extract did not produce significant effects on anxiety states and short-time memory.[147] Acute administration of valerian does not have mood-altering or psychomotor/ cognitive effects based on the study of Gutierrez *et al.* (2004).[148] The effects of valerian, propranolol, and their combination on activation, performance, and mood of healthy volunteers under social stress conditions had been reported.[149] In another study of Glass *et al.* (2003) revealed that valerian was not different from placebo on any measure of psychomotor performance or sedation.[150-151] Minidose valerian may play a role in saving injured neurons of the hippocampus by promoting the level of 5-hydroxytryptamine and cell proliferation in the hippocampus of depressive rats.[152] Stress-induced plasma corticosterone levels was downregulated by valerian oil, but not, 1,3-dimethoxy-5-methylbenzene.[153] Junior *et al*. (2010) tested the effect of a compound combining *V. officinalis* and *Passiflora alata* extracts on habituation of spontaneous locomotor activity in mice (Fig. 5). It was also found out in this study that *V. officinalis* and *P. alata* compound did not induce amnesia.[154]

Spasmolytic

According to Hendriks *et al.* 1981, the component compounds of valerian such as valerenic acid and the esters of eugenyl and isoeugenyl are spasmolytic.[155] Krieglstein and Grusla (1988) evaluated the pharmacological influence of valerian components on cerebral glucose turnover and the effect on cerebral blood supply.[156] A possible mechanism of action may relate to the interaction of the metabolism of gamma-aminobutyric acid in the brain with valerian constituents.[118-119,157]

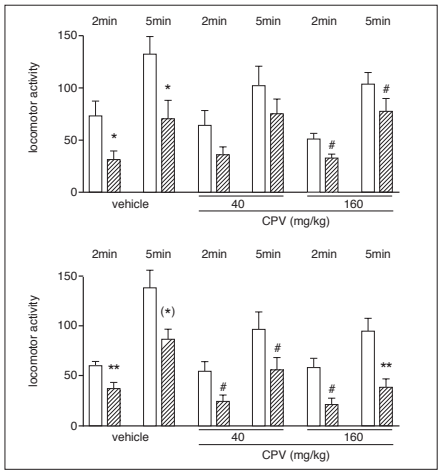


Figure 5. *Effects of Passiflora-Valeriana extract combination (CPV), and its vehicle (both p.o, 30 min before training), on habituation of spontaneous locomotor activity in mice between training session (white bars) and test session (hatched bars). Interval between sessions was 24 h. Upper panel: acute treatment (n=10-11 mice/ group); lower panel: chronic (15 days) treatment (n=8-12 mice/ group). The results are expressed as mean ± SEM of the number of beam interruptions recorded at 2 and 5 min of each session. (*) 0.06>p>0.05 Vs training session of the same group; # p<0.01 Vs training session of the same group; ** p<0.001 vs. training session of the same group (Student t test for repeated measures.*[154]

Effect on xenobiotic metabolism

In the study of Donovan *et al.* (2004), oral administration of two 500-mg valerian tablets nightly for two weeks in 12 healthy volunteers, had minimal effects on CYP3A4 activity and no effect on CYP2D6 activity.[158] Extracts of *Valeriana* as well as a fish oil preparation were potent inhibitors of tested enzymes based on the *in vitro* evaluation of potential for cytochrome P450 enzyme inhibition from herbals and other natural remedies.[159-160] The inhibitory effects of valerenic acid on glucuronidation were evaluated in human liver microsomes and with expressed uridine 5'-diphosphate-glucuronosyltransferases.[161] Extracts from *Centella asiatica* (gotu kola) and *V. officinalis* stimulated glutamic acid decarboxylase activity by over 40% at a dose of 1 mg/mL.[162]

Anticonvulsive/muscle relaxant/ antispasmodic effects

The root extract (Valdispert) increases thiopental sleeping-time and reduces mouse movement. It has moderate anti-convulsive property compared with diazepam and chlorpromazine.[163] Valerian was found to possess an anticonvulsant effect, but the uncertain chemical composition and content of valerian preparations, and their odor and taste, made it unlikely that they could ever prove satisfactory in widespread use.[31,164-165] The anticonvulsant & anxiolytic effects of *V. edulis* roots in several experimental models has been revealed.[166-167] According to Krystal and Ressler 2001, valerian preparations which have sedative & muscle-relaxant effects may have a mechanism of action and clinical characteristics that differ from the benzodiazepine-related sedative/ hypnotics, making them more suitable for long-term use.[168] Valtrate, Isovaltrate, and the essential oil compound valeranone at 10(-5) M concentrations relaxed muscle cells.[169]

Anesthetic effects

Rats given a combination of midazolam and valerian took longer to emerge from anesthesia.[170] It has been shown in rat brainstem preparation that effects of valerian potentiate the effects of anesthetics that act on GABA receptors and presurgical valerian use may cause interaction.[171] The inhibiting effect in GABA uptake and in decreasing the intracellular content of amino acid neurotransmitters in crude synaptosomes of rat had been shown by the methanolic extract of *V. adscendens*.[172]

Anti-coronary-spastic and anti-bronchospastic activities

Using the ethanolic and aqueous extracts of *V. officinalis* L. roots, its anticoronary-spastic and antibroncho-spastic activities were investigated in anaesthetized guinea-pigs and the results correlated with the qualitative/quantitative chemical composition of the extracts.[173] Valerian root extract was found to be a potent smooth muscle dilator in the feline pulmonary vascular bed and has vasodilatory effects as well.[174]

Effects on orofacial dyskinesia

In an animal model of orofacial dyskinesia, the effects of *V. officinalis* induced by long-term treatment with haloperidol was examined with inconclusive results.[175]

Effects on natural killer(Nk) cell activity

The effect of valerian on NK cell activity in male Sprague-Dawley rats undergoing abdominal surgery was examined.[176]

Anti-ischemic effects

Study suggests that chlorophyll and aqueous extracts of *V. wallichii* prevent ischaemia-reperfusion induced cerebral injury in mice with comparable potency.[177]

Adenosine A1 receptor agonist

Valerian and the fixed valerian hop extract combination Ze 91019 seems to cause the change of spectral power acting as an adenosine A1 receptor agonist in freely moving rats.[178-182] Results showed that the common use of hydrophilic, but not lipophilic valerian extracts as mild sleep-inducing agents is consistent with the opposite actions of hydrophilic and lipophilic extracts on adenosine receptors.[183] Comparison of the action of a methanol, ethanol, and an extract macerated with ethylacetate from roots of valerian on postsynaptic potentials in cortical neurons was studied by Sichardt *et al.* (2007).[184] Psychoactive herbal extracts from *Hypericum, Passiflora* and *Valeriana,* and various combinations thereof revealed a receptor-specific and concentration-dependent inhibition of the firing patterns.[185]

Effects on morphine withdrawal syndrome

In the study of Sharifzadeh *et al*. (2006) found that extracts of *V. officinalis* L. could affect morphine withdrawal syndrome via possible interactions with inhibitory neurotransmitters in nervous system on naloxone-induced jumping in morphine-dependent mice.[186]

Anti-cholesterolemic

It was found out that *V. officinalis* var *latifolia* reduced the serum levels of total cholesterol, low density lipoprotein, urinary albumin and serum creatinine in dietary-induced hypercholesterolemic male Wistar rats.[187]

Anti-hypersensitivity

Exposure of C57BL/6 mice to the odorants, terpinyl acetate and valerian oil, had minor effects on the contact hypersensitivity reaction.[153] It was also used as natural premedication for mast cell proliferative disorders.[188]

Induced pleasure effects

There was a decreased pleasure response to valerian seen in cats after gamma irradiation.[189]

Anti-aging/anti-neurodegenerative effects/antioxidant

The introduction of a new relevant use of valerian alcoholic extract to prevent neuronal degeneration in aging or neurodegenerative disorders was reported.[190] It is also known to have antioxidant property.[31]

Immune- modulation

The pectic polysaccharide-rich complex from *Valeriana* stimulated immune function of bone marrow cells.[191] Cardiovascular agents (valocordin, valerian, ouabain, and digoxin) synergize gamma radiation inhibition of proliferation of human lymphoid cells.[192] It has been demonstrated the potential cytoprotective effects of aqueous extract of *Valeriana officinalis* on rotenone-induced apoptosis in human neuroblastoma SH-SY5Y cells.[193] EtOAc extract of the underground parts of *Valeriana officinalis* showed inhibitory activity against NF-kappaB at 100 microg/mL in the IL-6/Luc assay on HeLa cells and provided protection against excitotoxicity in primary brain cell cultures at micromolar concentrations.[194] Significant immunostimulatory activities in mitogenic and comitogenic thymocyte tests was exhibited by the water-soluble polysaccharide fractions from both the conventional and ultrasonical experiments.[63]

Antimicrobial

Valtrate was found to inhibit the p-24 production of HIV-1 virus without showing any cytotoxicity against the host MT-4 cells.[25] Among 2 Valerian cultivars, oil of cultivar Select had antimicrobial effect against *Aspergillus niger*, *Escherichia coli, Staphylococcus aureus,* and *Saccharomyces cerevisiae* while cultivar Anthose showed low or no activity suggesting that inhibitory activity of valerian oil depends on the cultivar and its development.[195] *V. wallachi* was also found to have antifungal effect against pathogenic fungi.[196] Lazar-Baker *et al*. (2011) showed that higher concentrations of *V. officinalis* are needed to reduce significant fungal growth.[197]

Antihyperactivity

Valerian is just one approach to the treatment of childhood hyperactivity and can be used for different physiological actions.[198]

Nematicidal

Nematicidal activity against *Bursaphelenchus xylophilus* was achieved with essential oils of valerian.[199]

Antihypertensive

It is indicated in the study of Gilani *et al.* (2005) that the antispasmodic and hypotensive effects of *V. wallichii* may be mediated through K(ATP) channel activation, which justifies its use in gastrointestinal and cardiovascular disorders.[167]

SAFETY

Houghton (1988) conducted cytotoxicity and mutagenicity studies in animal cells. It was found out that valepotriates have no antitumor effects. The concern about the long-term safety of valerian preparations has been aroused due to the laboratory studies confirming cytotoxicity of valepotriates. Future formulations may be required to contain lower levels of valepotriates.[119] However, *V. officinalis* preparations are considered safe despite the known *in vitro* cytotoxic activity of valepotriates.[157] Acute side effects have not been reported. A study by Tufik, *et al.* (1984) examined the effects of valepotriates in female rats and their offspring. They found out that it did not produce changes in the average length of the estral cycle, nor the number of estrous phases and was deemed innocuous to pregnant rats and their offspring.[200]

In the United States, valerian is approved as a GRAS (generally recognized as safe) food ingredient. Its essential oil and extracts are used as flavoring components in alcoholic and nonalcoholic beverages, baked goods, gelatins, puddings, frozen dairy desserts, candy, and meat products at an average maximum level of 0.01 percent.[124] A Commission E phytomedicine monograph in Germany allows use of valerian in sedative and sleep-inducing preparations for states of excitation, and difficulty in falling asleep due to nervousness.[10] Valerian may potentiate the effects of antiepileptic medications, increasing their sedative and cognitive effects.[201-202]

Myasaka *et al.* (2006) investigated the effectiveness and safety of valerian for treating anxiety disorders.[131] In an open, multicentre study involving children under 12 years suffering from restlessness & nervous dyskoimesis confirmed that the combination of valerian/lemon balm preparation was effective and well tolerated.[203] It has also been reported that valerian can interact with the perioperative period among patients presenting for anaesthesia.[204-205] However, it is used as an herbal medications in the perioperative orthopedic surgery patient.[206]

It has been found out that valerian is also safe on human male sterility upon administration at dose levels corresponding to approximately 3 times the human daily dose.[207] It was found to be safe and effective for relieving menopausal symptoms including hot flashes and sleep disturbance in healthy postmenopausal women.[208] It has been used by Italian women to stimulate the immune system and to cure respiratory problems.[209] It has been found out also that the metal content of root extract is below toxic levels.[51] According to Larimore and O'MathÃºna (2004), herbal products like this should be regulated for quality control.[210]

ADVERSE EFFECTS AND TOXICITY

Valerian was given a class 1 safety rating, indicating that it is a safe herb with a wide dosage range by the American Herbal Products Association (AHPA).[2] However, some people experience adverse reactions to valerian. They suddenly feel nervous, anxious and restless after taking the herb and may experience heart palpitations rather than feeling the calming or sleep-inducing effects.[2] Serious withdrawal symptoms may occur when it is stopped abruptly in some cases of long-term use.[2]

Valerian should not be used by pregnant or breastfeeding women. It should not be used while operating heavy machinery, while driving, or engaging in other activities which require one to be alert due to its tranquilizing effects. Those taking valerian in combination with skullcap, another herb commonly used for anxiety, and those with liver disease are also warned.[2] Those taking anesthesia, sedatives or anti-anxiety medications should not use valerian without first consulting a healthcare practitioner.[2]

Though there were studies claiming for the safety and effectiveness of valerian, its adverse effects were also reviewed.[97,106,211] In fact, it was found out it has hepatotoxic effect.[212-213] Higher doses of products containing pseudoephedrine or valerian were associated with self-reported anxiety.[214] A patient with cholestatic hepatitis and acute Epstein-Barr virus infection with atypical lymphocytes and positive anti-VCA IgM was described to experience taking drugs like ibuprofen, paracetamol and valerian.[215] In the study of Malekzadeh *et al.* (2005) valerian increases the risk of breast cancer or interact with tamoxifen or aromatase inhibitors.[216] Alcohol abuser taking valerian and gingko biloba exhibited changes in mental status.[217] Valerian is beneficial for insomnia, but there is

no long-term safety data.[218] Valerian have been used for centuries and they appear to provide benefits in treating or preventing illness and were considered safe for use by most patients, but the supporting evidence is inconclusive in some cases.[219] It is in this particular reason why physicians should not encourage the use of valerian, for the treatment of anxiety based on small or inconsistent effects observed in a few studies, as suggested by review on herbal and dietary supplements for treatment of anxiety disorders.[220]

However, consumption of up to 65 times the human dose of the valerian extract supplied by Mediherb did not have an adverse reproductive outcome in rats based on a preliminary study.[221] Also, *V. officinalis* showed no genotoxic effects using Somatic Mutation And Recombination Test in *Drosophila melanogaster.*[222] In another study, the genotoxic effects of valerian in somatic and germ cells of mice were determined and the role of epigenetic mechanisms was investigated.[223] Farmers cultivating valerian could be exposed during processing of valerian roots to large concentrations of endotoxin, dust, and airborne microorganisms posing a risk of work-related respiratory disease.[224] Valerian-hops extract can cause drowsiness.[225] Increase in rat bile flow after acute PO and increase in alkaline phosphatase after chronic PO were demonstrated in an *in vitro* toxicity assay.[226] There are several reports on valerian root toxicity which includes nephrotoxicity, headaches, chest tightness, mydriasis, abdominal pain and tremor of the hands and feet.[227] "Sleep-Qik"(valerian dry extract 75 mg, hyoscine HBr 0.25 mg, cyproheptadine HCl 2 mg) is associated with anticholinergic poisoning and CNS depression.[228] An individual taking 20 times the normal dose had mild symptoms which resolved within 24 h.[229] Baldrinals, metabolites of valtrate and isovaltrate, but not dihydro-valtrate, appears to be mutagenic in the sensitive *Salmonella* assay.[230] High concentrations of dichloromethane extracts of valerian(DEV) induced DNA damage in human endothelial ECV304 cells, was mainly through epigenetic mechanisms, and at low doses DEV did not appear to have any genotoxicity in ECV304 cells.[231]

STANDARDIZED TO FULL SPECTRUM ACTIVITY PROFILE[232]

Valerenic acids (from Valerian) 1.8 mg

DOSAGE[232-233]

2 liquid Phyto-Caps, with warm water; 300-600mg; 2-3g dried valerian herbal root soaked in 1 cup hot water in 10-15 min

DURATION OF USE[232]

4-6 months

BEST TAKEN [232-233]

30 min-2 h before bedtime

COMPLEMENTARY HERBS/ FORMULAS[232]

Valerian/ Poppy Supreme, Skullcap/ St. John's Wort Supreme, Hops, Passionflower, Kava, Chamomile

SAFETY EVALUATIONS/ CONTRAINDICATIONS[232]

Do not use during pregnancy and lactation.

DRUG INTERACTIONS

Valerian has been found out to have adverse interactions with haloperidol.[234] However, in the study of Ugalde *et al.* (2005), it was found that valerian extract did not potentiate in mice the sedative effect of commonly prescribed CNS depressant drugs like haloperidol, diazepam, buspirone, pentobarbital, diphenhydramine and ethanol as expected.[235] Psychiatric patients treated with valerian need intensive medical advice and supervision.[236]

It was also investigated for its *in vitro* inhibitory potential of CYP1A2, CYP3A4, and CYP2D6 activity mediated metabolism and P-glycoprotein efflux transport activity.[237-239] Its potential for interaction accounted for 68% of the potential clinically significant interactions.[240-243] Valerian and rose inhalation significantly prolonged the pentobarbital-induced sleeping time based on the examination of the effects of odorant inhalation on the sleep-wake states in rats.[244] The interactions of commercial valerian extracts with GABA(A) receptors were examined using [3H]flunitrazepam binding as an indicator.[245] Its interaction with conventional drug therapies used for the treatment of dementia has been described also.[246] High dosage of Valdispert'balans' (a combination of valerian extract and hypericin)developed acute mania and psychosis in a patient with no psychiatric history.[247] Use of *Valeriana officinalis* should be limited, or completely excluded in cases of simultaneous therapy with warfarin, hepatotoxic agents, phenelzin sulphate, phenytoin, and MAOI inhibitors.[248]

Consult a physician if you are taking any pharmaceutical drugs. Do not take it with alcohol, benzodiazipines like alprazolam (xanax), clonazepam (Klonopin), diazepam (Valium), lorazepam (Ativan), midazolam (Versed), temazepam (Restoril), triazolam (Halcion), and others; CNS depressants like pentobarbital (Nembutal), phenobarbital (Luminal), secobarbital (Seconal), thiopental (Pentothal), fentanyl (Duragesic, Sublimaze), morphine, propofol (Diprivan), and others; Medications changed by the liver (Cytochrome P450 3A4 (CYP3A4) substrates) like lovastatin (Mevacor), ketoconazole (Nizoral), itraconazole (Sporanox), fexofenadine (Allegra), triazolam (Halcion), and many others; herbs and supplements with sedative effects include calamus, California poppy, catnip, hops, Jamaican dogwood, kava, L-tryptophan, melatonin, sage, SAMe, St. John's wort, sassafras, skullcap, and others.[232,249-250]

FUTURE DIRECTIONS

Valerian is a good example of both the negative and positive aspects of herbal medication. The considerable variation in its composition and the instability of some of its constituents pose serious problems for standardization but the range of components which contribute to its overall activity suggest that it may correct a variety of underlying causes of conditions.[13] Though, there are many compounds isolated from valerian that may be useful in the treatment of anxiety, stress, and insomnia but further studies are required to determine their relative roles for such indications.

Andreatini *et al.* (2002) suggested that the valepotriates may have a potential anxiolytic effect on the psychic symptoms of anxiety. However, results must be viewed as preliminary since the number of subjects per group was very small.[129] The evidence for single-dose effect is contradictory. Valerian is also used in patients with mild anxiety, but the data supporting this indication are limited. Since only a sparse and small study is currently available, there is insufficient evidence to draw any conclusion about the efficacy or safety of valerian compared with placebo or diazepam for anxiety disorders. Randomized controlled trials (RCTs) involving larger samples

and comparing valerian with placebo or other interventions used to treat anxiety disorders, such as antidepressants, are needed.[131]

Studies on valerian differ greatly with respect to measures, design, and preparations used. However, valerian is widely and traditionally used. Therefore, more research is required into its effective therapeutic dose, types of valerian preparation, optimum period of use for therapeutic effect, and its possible contraindications.

Despite subjective improvement, valerian did not produce faster sleep onset based on sleep data shown by Hadley and Petry (2003); the increase in alpha count compared with normal controls may point to residual hyperarousabilty, which is known to play a role in insomnia. Nonetheless, data on the extent to which a sedative drug can improve alpha sleep EEG are lacking.[100] Likewise, over-the-counter agents such as valerian and melatonin may be useful in alleviating mild, short-term insomnia, but further clinical trials are required to fully evaluate their safety and efficacy.[102,251]

Translating the study results into effective treatments is difficult due to the chemical complexity of products, lack of standardization, and paucity of well-controlled studies although evidence on efficacy of herbal preparations in treating psychiatric conditions is growing.[252] According to Meolie *et al.* (2005), there is a preliminary but conflicting evidence that *V. officinalis* L. and first-generation histamine-1-receptor antagonists have efficacy as mild hypnotics over short-term use.[251] Although the adverse effect profile and tolerability of this herb are excellent, long-term safety studies are lacking.[100,129] Thus, further studies addressing this issue are warranted.

Conclusively, the vast majority of the research relating to valerian briefly reviewed above is conducted in an entirely discrete discipline. In terms of research pertinent to brain function, the vast majority is basic laboratory research that requires more research application to unravel the marvels of valerian. The curiosity of people as to why plant chemicals modulate brain function can only serve to highlight the core of this tremendous research effort, with the blending of constructs from divergent biomedical disciplines serving an intellectual synergism that might push it to a higher ground.

Author's background

Prof. Joewel Tarra Baibado *is a doctor of Public Health Medical Microbiology student at the University of the Philippines. He obtained his Master of Science in Biology (Microbiology), BS in Biology, and Professional Education from the same university. He is an assistant professor of medical microbiology, parasitology and human biology at Iloilo Doctors' College, College of Sciences and Nursing in Philippines. His research interests include screening of antimicrobial properties of bioactive compounds of Philippine mangroves and indigenous Philippine herbs. His email address: Joewel20022002@yahoo.com; jbaibado2@cityu.edu.hk*

Dr. Cheung Hon-Yeung*, who is an associate professor of Pharmaceutical Microbiology & Biotechnology at the City University of Hongkong, is a manufacturing pharmacist and biotechnologist. He has more than 30 years of work experiences in industries, academic and consultancy jobs. He was an expert witness in court and a member of the Biotechnology Committee for Hong Kong and Shenzheng Government. Dr Cheung has published more than 190 papers and articles in many prestigious international journals. His email address: bhhonyun@cityu.edu.hk*

References

1. Thorpe Benjamin. Northern Mythology. 2: 64-65
2. Donaldson J (2010). Insight Journal. http://www.anxiety-and-depression
3. Ockendon DL (1976). Valeriana. in Tutin TG, Heywood VH, Burges NA, Moore DM, Valentine DH, Walters SM, Webb DA (ed). *Flora Europaea* 4:53. New York: Cambridge University Press.
4. Fernald ML (1950). Gray's Manual of Botany. 8th ed. New York: D. Van Nostrand.
5. Mabberly DJ (1987). The Plant Book. New York: Cambridge University Press.
6. Huang B, Zheng H, Qin L, Zheng Q, Xin H (2004). [Investigation on Resource of Genus *Valeriana* in China]. [Article in Chinese] *Zhong Yao Cai.* 27(9):632-634.
7. Castillo P, Zamilpa A, MÃ¡rquez J, HernÃ¡ndez G, Lara M, Alvarez L (2002). Comparative Study of Differentiation Levels and Valepotriate Content of *In vitro* Cultures and Regenerated and Wild Plants of *Valeriana edulis* sp.*procera. J Nat Prod.* 65(4):573-575.
8. Foster, S (1990). Valerian. *American Botanical Council*. Botanical Series No. 312.
9. http://www.lib.njutcm.edu.cn/yaodian/jp/14data/Part-II/Japanese_Valerian.pdf
10. Blumenthal M *et al.*(1999). The Complete German E Monographs Therapeutic Guide to Herbal Medicines. Austin, Texas, USA: American Botanical Council
11. http://chestofbooks.com/health/materia-medica-drugs/Manual-Pharmacology/Valeriana-Valerian.html
12. Lindahl O, Lindwall L (1989). Double Blind Study of Valerian Preparation. *Pharmacol Biochem Behav*. 32(4):1065-1066
13. Houghton PJ (1999). The Scientific Basis for the Reputed Activity of Valerian. *J Pharm Pharmacol.* 51(5):505-512.
14. Benke D, Barberis A, Kopp S, Altmann KH, Schubiger M, Vogt KE, Rudolph U, MÃ¶hler H (2009). GABA A Receptors as *In vivo* Substrate for the Anxiolytic Action of Valerenic Acid, a Major Constituent of Valerian Root Extracts. *Neuropharmacol.* 56(1):174-181. Epub 2008 Jun 17.
15. Trauner G, Khom S, Baburin I, Benedek B, Hering S, Kopp B (2008). Modulation of GABAA Receptors by Valerian Extracts is Related to the Content of Valerenic Acid. *Planta Med.* 74(1):19-24. Epub 2007 Dec 19.
16. Khom S, Baburin I, Timin E, Hohaus A, Trauner G, Kopp B, Hering S (2007). Valerenic Acid Potentiates and Inhibits GABA(A) Receptors: Molecular Mechanism and Subunit Specificity. *Neuropharmacol.* 53(1):178-187. Epub 2007 May 13.
17. Dietz BM, Mahady GB, Pauli GF, Farnsworth NR (2005). Valerian Extract and Valerenic Acid are Partial Agonists of the 5-HT5a Receptor *In vitro. Brain Res Mol Brain Res*. 138(2):191-197.
18. Granger RE, Campbell EL, Johnston GA (2005). (+)- And (-)-Borneol: Efficacious Positive Modulators of GABA Action at Human Recombinant *alpha1beta2gamma2L* GABA(A) Receptors. *Biochem Pharmacol.* 69(7):1101-1011.
19. Simmen U, Saladin C, Kaufmann P, Poddar M, Wallimann C, Schaffner W (2005). Preserved Pharmacological Activity of Hepatocytes-Treated Extracts of Valerian and St. John's Wort. *Planta Med.* 71(7):592-598.
20. Kennedy D, Wightman E (2011). Herbal Extracts and Phytochemicals: Plant Secondary Metabolites and the Enhancement of Human Brain Function. *Adv Nutr 2: 32-50, 2011*
21. http://www.sigmaaldrich.com
22. FernÃ¡ndez S, Wasowski C, Paladini AC, Marder M (2004). Sedative and Sleep-Enhancing Properties of Linarin, a Flavonoid-Isolated from *Valeriana officinalis. Pharmacol Biochem Behav.* 77(2):399-404.
23. Marder M, Viola H, Wasowski C, FernÃ¡ndez S, Medina JH, Paladini AC (2003). 6-Methylapigenin and Hesperidin: New *Valeriana* Flavonoids with Activity on the CNS. *Pharmacol Biochem Behav.* 75(3):537-545.
24. Wasowski C, Marder M, Viola H, Medina JH, Paladini AC (2002). Isolation and Identification of 6-Methylapigenin, a Competitive Ligand for the Brain GABA(A) Receptors, from *Valeriana wallichii. Planta Med.* 68(10):934-936.
25. Murakami N, Ye Y, Kawanishi M, Aoki S, Kudo N, Yoshida M, Nakayama EE, Shioda T, Kobayashi M (2002). New Rev-Transport Inhibitor with Anti-HIV Activity from *Valerianae radix. Bioorg Med Chem Lett.* 12(20):2807-2810.
26. Joshi VC, Navarrete A, Khan IA (2005). Authentication of *Valeriana procera* Kunth and Comparative Account of Five *Valeriana* Species. *J AOAC Int.* 88(6):1621-1625.
27. Mathela CS, Chanotiya CS, Sammal SS, Pant AK, Pandey S (2005). Compositional Diversity of Terpenoids in the Himalayan *Valeriana* Genera. *Chem Biodivers.* 2(9):1174-1182.
28. Pullela SV, Choi YW, Khan SI, Khan IA (2005). New Acylated Clionasterol Glycosides from *Valeriana officinalis. Planta Med*. 71(10):960-961.
29. Shi JL, Liu Y, Xiao PG (2005). [Studies on HPLC Fingerprint of the Hydrophilic Constituents of *Valeriana* Medicinal Plants]. [Article in Chinese] *Zhongguo Zhong Yao Za Zhi.* 30(6):426-429.
30. Goppel M, Franz G (2004). Stability Control of Valerian Ground Material and Extracts: a New HPLC-Method for the Routine Quantification of Valerenic Acids and Lignans. *Pharmazie.* 59(6):446-452.
31. Piccinelli AL, Arana S, Caceres A, di Villa Bianca R, Sorrentino R, Rastrelli L (2004). New Lignans from the Roots of *Valeriana prionophylla* with Antioxidative and Vasorelaxant Activities. *J Nat Prod.* 67(7):1135-1140.
32. Srikrishna A, Satyanarayana G (2004). Enantioselective Total Synthesis of Valerianandoids A-C. *Org Lett.* 6(14):2337-2339.
33. Tang YP, Liu X, Yu B (2003). Two New Flavone Glycosides from *Valeriana jatamansi. J Asian Nat Prod Res*. 5(4):257-261.
34. Chen L, Qin L, Zheng H, Nian H, Guo C, Zhang C (2002). [Interspecific and Intraspecific Comparison of Valepotrates Contents in Three *Valeriana* Plants]. [Article in Chinese] *Zhong Yao Cai.* 25(4):237-238.
35. Dharmaratne HR, Nanayakkara NP, Khan IA (2002). (-)-3 *Beta*,4 *Beta*-Epoxyvalerenic Acid from *Valeriana officinalis. Planta Med*. 68(7):661-662.
36. Silva AL, Rech SB, von Poser GL (2002). Quantitative Determination of Valepotriates from *Valeriana* Native to South Brazil. *Planta Med.* 68(6):570-572.
37. Tang Y, Liu X, Yu B (2002). Iridoids from the Rhizomes and Roots of *Valeriana jatamansi. J Nat Prod.* 65(12):1949-1952.
38. Yu LL, Han CR, Huang R, Lv YP, Gui SH, Chen YG (2006). A New Iridoid Tetraester from *Valeriana jatamansi. Pharmazie.* 61(5):486-488.
39. Mikell JR, Ganzera M, Khan IA (2001). Analysis of Sesquiterpenes in *Valeriana officinalis* by Capillary Electrophoresis. *Pharmazie.* 56(12):946-948.
40. Valachovic P, Pechova A, Mason TJ (2001). Towards the Industrial Production of Medicinal Tincture by Ultrasound Assisted Extraction. *Ultrason Sonochem.* 8(2):111-117.
41. Bicchi C, Drigo S, Rubiolo P (2000). Influence of Fiber Coating in Headspace Solid-Phase Microextraction-Gas Chromatographic Analysis of Aromatic and Medicinal Plants. *J Chromatogr A.* 892(1-2):469-485.
42. Gao XQ, BjÃ¶rk L (2000). Valerenic acid Derivatives and Valepotriates among Individuals, Varieties and Species of *Valeriana. Fitoterapia.*71(1):19-24.

43. Paul (2001). *Valeriana officinalis* Herb Med. http://www.scribd.com/doc/26830396/VALERIAN-Valeriana-Officinalis-HerbMed

44. Cavadas C, AraÃºjo I, Cotrim MD, Amaral T, Cunha AP, Macedo T, Ribeiro CF (1995). *In vitro* Study on the Interaction of *Valeriana officinalis* L. Extracts and their Amino Acids on GABAA receptor in Rat Brain. *Arzneimittelforschung*. 45(7):753-755.

45. Kim HJ, Baburin I, Khom S, Hering S, Hamburger M (2008). HPLC-Based Activity Profiling Approach for the Discovery of GABAA Receptor Ligands Using an Automated Two Microelectrode Voltage clamp assay on *Xenopus* oocytes. *Planta Med.* 74(5):521-526.

46. Safaralie A, Fatemi S, Sefidkon F (2008). Essential Oil Composition of *Valeriana officinalis* L. Roots Cultivated in Iran. Comparative Analysis Between Supercritical CO_2 Extraction and Hydrodistillation. *J Chromatogr A.* 1180(1-2):159-164. Epub 2007 Dec 14.

47. Jiang X, Zhang JC, Liu YW, Fang Y (2007). [Studies on Chemical Constituents of *Valeriana officinalis*]. [Article in Chinese] *Zhong Yao Cai.* 30(11):1391-1393.

48. Mathela CS, Chanotiya CS, Sati S, Sammal SS, Wray V (2007). Epoxysesquithujene, a Novel Sesquiterpenoid from *Valeriana hardwickii* var. *hardwickii. Fitoterapia.* 4:279-282. Epub 2007 Apr 11.

49. Pobozniak M. (2007) Analysis of the Thrips Fauna (Thysanoptera) on Flowers of Herbs. Commun *Agric Appl Biol Sci.* 72(3):495-501.

50. Xu YM, McLaughlin SP, Gunatilaka AA (2007). Sorbifolivaltrates A-D, Diene Valepotriates from *Valeriana sorbifolia*(1). *J Nat Prod.* 70(12):2045-2048. Epub 2007 Dec 6.

51. Grippo AA, Hamilton B, Hannigan R, Gurley BJ (2006). Metal content of Ephedra-Containing Dietary Supplements and Select Botanicals. *Am J Health Syst Pharm*. 63(7):635-644.

52. Arce S, Cerutti S, Olsina R, Gomez MR, MartÃnez LD (2008). Determination of Metal Content in Valerian Root Phytopharmaceutical Derivatives by Atomic Spectrometry. *J AOAC Int.* 88(1):221-225.

53. Guo Y, Xu J, Li Y, Yamakuni T, Ohizumi Y (2006). Three-Membered Ring Sesquiterpenoids with NGF-Potentiating activity from the Roots of *Valeriana fauriei. Planta Med.* 72(4):373-375.

54. Guo Y, Xu J, Li Y, Watanabe R, Oshima Y, Yamakuni T, Ohizumi Y (2006). Iridoids and Sesquiterpenoids with NGF-Potentiating Activity from the Rhizomes and Roots of *Valeriana fauriei. Chem Pharm Bull* (Tokyo). 54(1):123-125.

55. Zhang ZX, Dou DQ, Liu K, Yao XS (2006). Studies on the Chemical Constituents of *Valeriana fauriei* Briq. *J Asian Nat Prod Res.* 8(5):397-400.

56. Navarrete A, Avula B, Choi YW, Khan IA (2006). Chemical Fingerprinting of *Valeriana* species: Simultaneous Determination of Valerenic Acids, Flavonoids, and Phenylpropanoids using Liquid Chromatography with Ultraviolet Detection. *J AOAC Int.* 89(1):8-15.

57. Slanc P, Ravnikar M, Strukelj B (2006). Identification of Individual Herbal Drugs in Tea Mixtures Using Restriction Analysis of ITS DNA and Real-Time PCR. *Pharmazie.* 61(11):912-915.

58. Anderson GD, Elmer GW, Kantor ED, Templeton IE, Vitiello MV (2005). Pharmacokinetics of Valerenic Acid after Administration of Valerian in Healthy Subjects. *Phytother Res.* 19(9):801-803.

59. Bello de Carvalho CM, Maurmann N, Luz DI, Fett-Neto AG, Rech SB (2004). Control of Development and Valepotriate Production by Auxins in Micropropagated *Valeriana glechomifolia. Plant Cell Rep.* 23(4):251-255. Epub 2004 Jul 14.

60. Boyadzhiev L, Kancheva D, Gourdon C, Metcheva D (2004). Extraction of Valerenic Acids from Valerian (*Valeriana officinalis* L.) Rhizomes. *Pharmazie.* 59(9):727-728.

61. Torrado JJ (2003). *In vitro* Release of Valerenic and Hydroxyvalerenic Acids from Valerian Tablets. *Pharmazie.* 58(9):636-638.

62. Shohet D, Wills RB, Stuart DL (2001). Valepotriates and Valerenic Acids in Commercial Preparations of Valerian Available in Australia. *Pharmazie*. 56(11):860-863.

63. HromÃ¡dkovÃ¡ Z, EbringerovÃ¡ A, Valachovic P (2002). Ultrasound-Assisted Extraction of Water-Soluble Polysaccharides from the Roots of Valerian (*Valeriana officinalis* L.). *Ultrason Sonochem.* 2002 Jan;9(1):37-44.

64. Politi M, Zloh M, Pintado ME, Castro PM, Heinrich M, Prieto JM (2009). Direct Metabolic Fingerprinting of Commercial Herbal Tinctures by Nuclear Magnetic Resonance Spectroscopy and Mass Spectrometry. *Phytochem Anal.* 20(4):328-334.

65. Duan XY, Gong ZF, Chen SH, Fang Y, Liu YW (2009). HPLC Fingerprint of the Antiarrhythmic Fraction of *Valeriana officinalis. Zhong Yao Cai.* 32(6):866-70.

66. Nell M, Wawrosch C, Steinkellner S, Vierheilig H, Kopp B, Lössl A, Franz C, Novak J, Zitterl-Eglseer K (2010). Root Colonization by Symbiotic Arbuscular Mycorrhizal Fungi Increases Sesquiterpenic Acid Concentrations in *Valeriana officinalis* L. *Planta Med.* 76(4):393-398. Epub 2009 Oct 6.

67. Wang PC, Ran XH, Chen R, Luo HR, Liu YQ, Zhou J, Zhao YX (2010). Germacrane-Type Sesquiterpenoids from the Roots of *Valeriana officinalis* var. *latifolia. J Nat Prod.* 73(9):1563-1567.

68. Del Valle-Mojica LM, Cordero-Hernández JM, González-Medina G, Ramos-Vélez I, Berríos-Cartagena N, Torres-Hernández BA, Ortíz JG (2011). Aqueous and Ethanolic *Valeriana officinalis* Extracts Change the Binding of Ligands to Glutamate Receptors. *Evid Based Complement Alternat Med.* 2011: 891819.

69. Diaper A, Hindmarch I (2004). A Double-Blind, Placebo-Controlled Investigation of the Effects of Two Doses of a Valerian Preparation on the Sleep, Cognitive and Psychomotor Function of Sleep-Disturbed Older Adults. *Phytother Res.* 18(10):831-836.

70. Dimpfel W, Suter A (2008). Sleep Improving Effects of a Single Dose Administration of a Valerian/Hops Fluid Extract - a Double Blind, Randomized, Placebo-Controlled Sleep-EEG Study in a Parallel Design Using Electrohypnograms. *Eur J Med Res.* 13(5):200-204.

71. Koetter U, Schrader E, Käufeler R, Brattström A (2007). A Randomized, Double Blind, Placebo-Controlled, Prospective Clinical Study to Demonstrate Clinical Efficacy of a Fixed Valerian Hops Extract Combination (Ze 91019) in Patients Suffering from Non-Organic Sleep Disorder. *Phytother Res.* 21(9):847-851.

72. Salter S, Brownie S (2010). Treating Primary Insomnia - the Efficacy of Valerian and Hops. *Aust Fam Physician*. 39(6):433-437.

73. Pallesen S, Bjorvatn B, Nordhus IH, Skjerve A (2002). Valerian as a Sleeping Aid? *Tidsskr Nor Laegeforen.* 122(30):2857-2859.

74. Krystal AD (2007). Treating the Health, Quality of Life, and Functional Impairments in Insomnia. *J Clin Sleep Med.* 3(1):63-72.

75. Oxman AD, Flottorp S, Hävelsrud K, Fretheim A, Odgaard-Jensen J, Austvoll-Dahlgren A, Carling C, Pallesen S, Bjorvatn B (2007). A Televised, Web-Based Randomised Trial of an Herbal Remedy (Valerian) for Insomnia. *PLoS One.* 2(10):e1040.

76. Tariq SH, Pulisetty S (2008). Pharmacotherapy for Insomnia. *Clin Geriatr Med.*24(1):93-105, vii.

77. Ziegler G, Ploch M, Miettinen-Baumann A, Collet W (2002). Efficacy and Tolerability of Valerian Extract LI 156 Compared with Oxazepam in the Treatment of Non-Organic Insomnia--a Randomized, Double-Blind, Comparative Clinical Study. *Eur J Med Res.* 7(11):480-486.

78. Füssel A, Wolf A, Brattström A (2000). Effect of a Fixed Valerian-Hop Extract Combination (Ze 91019) on Sleep Polygraphy in Patients with Non-Organic Insomnia: a Pilot Study. *Eur J Med Res.* 5(9):385-390.

79. Donath F, Quispe S, Diefenbach K, Maurer A, Fietze I, Roots I (2000). Critical Evaluation of the Effect of Valerian Extract on Sleep Structure and Sleep Quality. *Pharmacopsychiatry.* 33(2):47-53.

80. Leathwood PD, Chauffard F, Heck E, Munoz-Box R (1982). Aqueous Extract of Valerian Root (*Valeriana officinalis* L.) Improves Sleep Quality in Man. *Pharmacol Biochem Behav*. 17(1):65-71.

81. Giedke H, Breyer-Pfaff U (2000). Critical Evaluation of the Effect of Valerian Extract on Sleep Structure and Sleep Quality. *Pharmacopsychiatry*. 33(6):239.

82. Balderer G, Borbély AA (1985). Effect of Valerian on Human Sleep. *Psychopharmacology* (Berl). 1985;87(4):406-409.

83. Bent S, Padula A, Moore D, Patterson M, Mehling W (2006). Valerian for Sleep: a Systematic Review and Meta-analysis. *Am J Med.* 119(12):1005-1012.

84. Schmitz M, Jäckel M (1998). [Comparative Study for Assessing Quality of Life of Patients with Exogenous Sleep Disorders (Temporary Sleep Onset and Sleep Interruption Disorders) Treated with a Hops-Valerian Preparation and a Benzodiazepine drug]. [Article in German] *Wien Med Wochenschr.* 148(13):291-298.

85. Morin CM, Koetter U, Bastien C, Ware JC, Wooten V (2005). Valerian-Hops Combination and Diphenhydramine for Treating Insomnia: a Randomized Placebo-Controlled Clinical Trial. *Sleep.* 28(11):1465-1471.

86. Jacobs BP, Bent S, Tice JA, Blackwell T, Cummings SR (2005). An Internet-Based Randomized, Placebo-Controlled Trial of Kava and Valerian for Anxiety and Insomnia. *Medicine* (Baltimore). 84(4):197-207.

87. Oxman AD, Flottorp S, HÃ¥velsrud K, Fretheim A, Odgaard-Jensen J, Austvoll-Dahlgren A, Carling C, Pallesen S, Bjorvatn B (2007). A Televised, Web-Based Randomised Trial of an Herbal Remedy (valerian) for Insomnia. *PLoS One.* 2(10):e1040.

88. Brown RP, Gerbarg PL (2001). Herbs and Nutrients in the Treatment of Depression, Anxiety, Insomnia, Migraine, and Obesity. *J Psychiatr Pract.* 7(2):75-91.

89. Gyllenhaal C, Merritt SL, Peterson SD, Block KI, Gochenour T (2000). Efficacy and Safety of Herbal Stimulants and Sedatives in Sleep Disorders. *Sleep Med Rev.* 4(3):229-251.

90. Fugh-Berman A, Cott JM (1999). Dietary Supplements and Natural Products as Psychotherapeutic Agents. *Psychosom Med.* 61(5):712-728.

91. Coxeter PD, Schluter PJ, Eastwood HL, Nikles CJ, Glasziou PP (2003). Valerian does not Appear to Reduce Symptoms for Patients with Chronic Insomnia in General Practice using a series of Randomised n-of-1 Trials. *Complement Ther Med.* 11(4):215-222.

92. Gooneratne NS (2008). Complementary and Alternative Medicine for Sleep Disturbances in Older Adults. *Clin Geriatr Med.* 24(1):121-138, viii.

93. Waldschütz R, Klein P (2008). The Homeopathic Preparation Neurexan vs. Valerian for the Treatment of Insomnia: an Observational Study. *ScientificWorldJournal.* 8:411-420.

94. Volz HP (2001). [Phytochemicals as Means to Induce Sleep]. [Article in German] *Z Arztl Fortbild Qualitatssich*. 95(1):33-34.

95. Stevinson C, Ernst E (2000). Valerian for Insomnia: a Systematic Review of Randomized Clinical Trials. *Sleep Med.* 1(2):91-99.

96. Taibi DM, Landis CA, Petry H, Vitiello MV (2007). A Systematic Review of Valerian as a Sleep Aid: Safe but not Effective. *Sleep Med Rev.* 11(3):209-230.

97. Francis AJ, Dempster RJ (2002). Effect of Valerian, *Valeriana edulis*, on Sleep Difficulties in Children with Intellectual Deficits: Randomised Trial. *Phytomedicine.* 9(4):273-279.

98. Poyares DR, Guilleminault C, Ohayon MM, Tufik S (2002). Can Valerian Improve the Sleep of Insomniacs after Benzodiazepine Withdrawal? *Prog Neuropsychopharmacol Biol Psychiatry.* 26(3):539-545.

99. Schmitz M, Jäckel M (1998). Comparative Study for Assessing Quality of Life of Patients with Exogenous Sleep Disorders (Temporary Sleep Onset and Sleep Interruption Disorders) Treated with a Hops-Valerian Preparation and a Benzodiazepine Drug. *Wien Med Wochenschr.* 148(13):291-298.

100. Hadley S, Petry JJ (2003). Valerian. *Am Fam Physician.* 67(8):1755-1758.

101. Wheatley D (2005). Medicinal Plants for Insomnia: a Review of their Pharmacology, Efficacy and Tolerability. J *Psychopharmacol.* (4):414-421.

102. Wagner J, Wagner ML, Hening WA (1998). Beyond Benzodiazepines: Alternative Pharmacologic Agents for the Treatment of Insomnia. *Ann Pharmacother*. 32(6):680-691.

103. Gessner B, Klasser M (1984). [Studies on the Effect of *Harmonicum Much* on Sleep using Polygraphic EEG Recordings]. [Article in German] *EEG EMG Z Elektroenzephalogr Elektromyogr Verwandte Geb*. 15(1):45-51.

104. Dominguez RA, Bravo-Valverde RL, Kaplowitz BR, Cott JM (2000). Valerian as a Hypnotic for Hispanic Patients. *Cultur Divers Ethnic Minor Psychol*. 6(1):84-92.

105. Bliwise DL, Ansari FP (2007). Insomnia Associated with Valerian and Melatonin Usage in the 2002 National Health Interview Survey. *Sleep.* 30(7):881-884.

106. Heiligenstein E, Guenther G (1998). Over-the-Counter Psychotropics: a Review of Melatonin, St John's Wort, Valerian, and Kava-kava. *J Am Coll Health.* 46(6):271-276.

107. Shimazaki M, Martin JL (2007). Do Herbal Agents have a Place in the Treatment of Sleep Problems in Long-Term Care? *J Am Med Dir Assoc.* 8(4):248-252. Epub 2007 Apr 18.

108. Herrera-Arellano A, Luna-Villegas G, Cuevas-Uriostegui ML, Alvarez L, Vargas-Pineda G, Zamilpa-Alvarez A, Tortoriello J (2001). Polysomnographic Evaluation of the Hypnotic effect of *Valeriana edulis* Standardized Extract in Patients Suffering from Insomnia. *Planta Med.* 67(8):695-699.

109. Schulz H, Stolz C, Müller J (1994). The Effect of Valerian Extract on Sleep Polygraphy in Poor Sleepers: a Pilot Study. *Pharmacopsychiatry.* 27(4):147-151.

110. Dorn M (2000). [Efficacy and Tolerability of Baldrian versus Oxazepam in Non-Organic and Non-Psychiatric Insomniacs: a Randomised, Double-Blind, Clinical, Comparative Study]. [Article in German] *Forsch Komplementarmed Klass Naturheilkd.* 7(2):79-84.

111. Ammer K, Melnizky P (1999). [Medicinal Baths for Treatment of Generalized Fibromyalgia]. [Article in German] *Forsch Komplementarmed.* 6(2):80-85.

112. Taibi DM, Bourguignon C, Taylor AG (2004). Valerian Use for Sleep Disturbances Related to Rheumatoid Arthritis. *Holist Nurs Pract.* 18(3):120-126.

113. Tokunaga S, Takeda Y, Niimoto T, Nishida N, Kubo T, Ohno T, Matsuura Y, Kawahara Y, Shinomiya K, Kamei C (2007). Effect of Valerian Extract Preparation (BIM) on the Sleep-Wake Cycle in Rats. *Biol Pharm Bull.* 30(2):363-366.

114. Shinomiya K, Fujimura K, Kim Y, Kamei C (2005). Effects of Valerian Extract on the Sleep-Wake Cycle in Sleep-Disturbed Rats. *Acta Med Okayama.* 59(3):89-92.

115. Gedevanishvili MD, Sikharulidze IS, Gogotidze NM (2006). [Toxicological Approach to Evaluation of Bioavailability of Powdered Medicinal Herbs]. [Article in Russian] *Georgian Med News*. (134):121-124.

116. Buchbauer G, Jäger W, Jirovetz L, Meyer F, Dietrich H (1992). Effects of Valerian Root Oil, Borneol, Isoborneol, Bornyl Acetate and Isobornyl Acetate on the Motility of Laboratory Animals (mice) After Inhalation. *Pharmazie.* 47(8):620-622

117. Hazelhoff B, Weert B, Denee R, and Malingre TM (1979). Isolation and analytical aspects of *Valeriana* compounds. *Pharm. Weekbl. Sci. Ed.* 1(4):956-964.

118. Hobbs, C (1989). Valerian *Valeriana officinalis*: A Literature Review. HerbalGram 21 (Fall): 19-34.-1990. Phu: Valerian and Other Anti-Hysterics in European and American Medicine (1733-1936). *Pharmacy in History* 32(3): 132-137.

119. Houghton, PJ (1988). The Biological Activity of Valerian and Related Plants. *J of Ethnopharmacol.* 22:121-142.

120. Gerhard U, Hobi V, Kocher R, König C (1991). [Acute Sedative Effect of a Herbal Relaxation Tablet as Compared to that of Bromazepam]. [Article in German] *Schweiz Rundsch Med Prax.* 80(52):1481-1486.

121. Della Loggia R, Tubaro A, Redaelli C (1981). [Evaluation of the Activity on the Mouse CNS of Several Plant Extracts and a Combination of Them]. [Article in Italian] *Riv Neurol.* 51(5):297-310.

122. Wheatley D (2001). Kava and Valerian in the Treatment of Stress-Induced Insomnia. *Phytother Res.* 15(6):549-551.

123. Werneke U, Turner T, Priebe S (2006). Complementary Medicines in Psychiatry: Review of Effectiveness and Safety. *Br J Psychiatry.* 188:109-121.

124. Leung AY, Foster S (1996). Encyclopedia of Common Natural Ingredients Used in Foods, Drugs, and Cosmetics. 2nd edition. New York: John Wiley and Sons.

125. Tyler V E (1993). The Honest Herbal. 3rd edition. Philadelphia: George F. Stickley Co.

126. Williamson EM, Evans FJ (1988). Potter's New Cyclopaedia of Botanical Drugs and Preparations. 8th ed. Saffron Walden: The C.W. Daniel Company Ltd.

127. Weiss RF (1988). Herbal Medicine (translated from German by A.R. Meuss). Beaconsfield, England: Beaconsfield Publishers Ltd.

128. Nencini C, Cavallo F, Capasso A, De Feo V, De Martino L, Bruni G, Giorgi G, Micheli L (2006). Binding Studies for Serotoninergic, Dopaminergic and Noradrenergic Receptors of *Valeriana adscendens* Trel. Extracts. *J Ethnopharmacol.* 108(2):185-187. Epub 2006 May 22.

129. Andreatini R, Sartori VA, Seabra ML, Leite JR (2002). Effect of Valepotriates (Valerian Extract) in Generalized Anxiety Disorder: a Randomized Placebo-Controlled Pilot Study. *Phytother Res.* 16(7):650-654.

130. Faustino TT, de Almeida RB, Andreatini R (2010). [Medicinal Plants for the Treatment of Generalized Anxiety Disorder: a Review of Controlled Clinical Studies]. *Rev Bras Psiquiatr.* 32(4):429-436. Portuguese.

131. Miyasaka LS, Atallah AN, Soares BG. (2006). Valerian for Anxiety Disorders. *Cochrane Database Syst Rev*. (4):CD004515.

132. Kennedy DO, Little W, Haskell CF, Scholey AB (2006). Anxiolytic Effects of a Combination of *Melissa officinalis* and *Valeriana officinalis* during Laboratory Induced Stress. *Phytother Res.* 20(2):96-102.

133. Bhattacharyya D, Jana U, Debnath PK, Sur TK (2007). Initial Exploratory Observational Pharmacology of *Valeriana wallichii* on Stress Management: a Clinical Report. *Nepal Med Coll J.* 9(1):36-39.

134. Geller SE, Studee L (2007). Botanical and Dietary Supplements for Mood and Anxiety in Menopausal Women. *Menopause.* 14(3 Pt 1):541-549.

135. Ustimov DIu (2005). [Preoperative Psychopharmacological Correction in Women with Focal Breast Diseases]. [Article in Russian] *Anesteziol Reanimatol.* (3):71-74.

136. Arushaian EB, Mastiagina OA, Mastiagin SS, Popova AP (2005). [Fluctuations of the Antianxiety Effect of Valerian and Grandaxin During Daytime Wakefulness in Humans with Different Chronotypes]. [Article in Russian] *Fiziol Cheloveka.*(2):135-137.

137. Müller D, Pfeil T, von den Driesch V (2003). Treating Depression Comorbid with Anxiety--Results of an Open, Practice-Oriented Study with St. John's Wort WS 5572 and Valerian Extract in High Doses. *Phytomedicine. Suppl* 4:25-30.

138. Weeks BS (2009). Formulations of Dietary Supplements and Herbal Extracts for Relaxation and Anxiolytic Action: Relarian. *Med Sci Monit.* 15(11):RA256-262.

139. Hattesohl M, Feistel B, Sievers H, Lehnfeld R, Hegger M, Winterhoff H (2008). Extracts of *Valeriana officinalis* L. s.l. show Anxiolytic and Antidepressant Effects but neither Sedative nor Myorelaxant Properties. *Phytomedicine.* 15(1-2):2-15.

140. Murphy K, Kubin ZJ, Shepherd JN, Ettinger RH (2010). *Valeriana officinalis* Root Extracts have Potent Anxiolytic Effects in Laboratory Rats.*Phytomedicine.* 17(8-9):674-678. Epub 2009 Dec 29.

141. Peeters E, Driessen B, Steegmans R, Henot D, Geers R (2004). Effect of Supplemental Tryptophan, Vitamin E, and a Herbal Product on Responses by Pigs to Vibration. *J Anim Sci.* 82(8):2410-2420.

142. Cropley M, Cave Z, Ellis J, Middleton RW (2002). Effect of Kava and Valerian on Human Physiological and Psychological Responses to Mental Stress Assessed under Laboratory Conditions. *Phytother Res*. 16(1):23-27.

143. Kutlubaev MA, Farkhutdinov RR, Akhmadeeva LR, Mufazalov AF (2005). Free Radical Oxidation in Rat Brain During Chronic Stress and Pharmacological Regulation of this Process. *Bull Exp Biol Med.* 140(4):416-418.

144. Vonderheid-Guth B, Todorova A, Brattström A, Dimpfel W (2000). Pharmacodynamic Effects of Valerian and Hops Extract Combination (Ze 91019) on the Quantitative-Topographical EEG in Healthy Volunteers. *Eur J Med Res*. 5(4):139-144.

145. Kuhlmann J, Berger W, Podzuweit H, Schmidt U (1999). The Influence of Valerian Treatment on "Reaction Time, Alertness and Concentration" in Volunteers. *Pharmacopsychiatry.* 32(6):235-241.

146. Santos MS, Ferreira F, Cunha AP, Carvalho AP, Ribeiro CF, Macedo T (1994). Synaptosomal GABA Release as Influenced by Valerian Root Extract--Involvement of the GABA Carrier. *Arch Int Pharmacodyn Ther*. 327(2):220-231.

147. Arushanian B, Mastiagina OA, Popova AP (2004). [Peculiarities in the Effect of Tofisopam and Valerian Extract on Short-term Memory and Anxiety States in Healthy Humans]. [Article in Russian] *Eksp Klin Farmakol.* 67(6):23-25

148. Gutierrez S, Ang-Lee MK, Walker DJ, Zacny JP (2004). Assessing Subjective and Psychomotor Effects of the Herbal Medication Valerian in Healthy Volunteers. *Pharmacol Biochem Behav.* 78(1):57-64.

149. Kohnen R, Oswald WD (1988). The Effects of Valerian, Propranolol, and their Combination on Activation, Performance, and Mood of Healthy Volunteers under Social Stress Conditions. *Pharmacopsychiatry.* 21(6):447-448.

150. Glass JR, Sproule BA, Herrmann N, Streiner D, Busto UE (2003). Acute Pharmacological Effects of Temazepam, Diphenhydramine, and Valerian in Healthy Elderly Subjects. *J Clin Psychopharmacol.* 2003 Jun;23(3):260-268.

151. Hallam KT, Olver JS, McGrath C, Norman TR (2003). Comparative Cognitive and Psychomotor Effects of Single Doses of *Valeriana officianalis* and Triazolam in Healthy Volunteers. *Hum Psychopharmacol.* 18(8):619-625.

152. Tang JY, Zeng YS, Chen QG, Qin YJ, Chen SJ, Zhong ZQ (2008). [Effects of Valerian on the Level of 5-Hydroxytryptamine, Cell Proliferation and Neurons in Cerebral Hippocampus of Rats with Depression Induced by Chronic Mild Stress]. [Article in Chinese] *Zhong Xi Yi Jie He Xue Bao.=J Chin integrat med*. 6(3):283-288.

153. Hosoi J, Tanida M, Tsuchiya T (2001). Mitigation of Stress-Induced Suppression of Contact Hypersensitivity by Odorant Inhalation. *Br J Dermatol.* 145(5):716-719.

154. Junior HS, Seniski G, da Cunha C, Aparecida-Audi E, Andreatini R (2010). The Combination of *Passiflora alata* and *Valeriana officinalison* Memory Tasks in Mice: Comparison with Diazepam. *Brazilian Arch of Bio & Tech* 53(6): 1343-1350.

155. Hendriks R, Bos, Allersma DP, Malingré ThM, Koster SJ (1981). Pharmacological Screening of Valerenal and some other Components of Essential Oil of *Valeriana officinalis. Planta Medica* 42:62-68.

156. Krieglstein J, Grusla D (1988). Central Depressant Constituent in Valerian. *Deutsche Apotheker Zeitung.* 40:2041-2046 (in German).

157. ESCOP (1990). "Proposal for a European Monograph on the Medicinal Use of Valerianae Radix (Valerian Root)". Brussels: European Scientific Cooperative for Phytotherapy.

158. Donovan JL, DeVane CL, Chavin KD, Wang JS, Gibson BB, Gefroh HA, Markowitz JS (2004). Multiple Night-Time Doses of Valerian *(Valeriana officinalis)* had Minimal Effects on CYP3A4 Activity and no Effect on CYP2D6 Activity in Healthy Volunteers. *Drug Metab Dispos*. 32(12):1333-1336. Epub 2004 Aug 24.

159. Strandell J, Neil A, Carlin G (2004). An Approach to the *In vitro* Evaluation of Potential for Cytochrome P450 Enzyme Inhibition from Herbals and other Natural Remedies. *Phytomedicine.* 11(2-3):98-104.

160. Lefebvre T, Foster BC, Drouin CE, Krantis A, Livesey JF, Jordan SA (2004). *In vitro* Activity of Commercial Valerian Root Extracts Against Human Cytochrome P450 3A4. *J Pharm Pharm* Sci. 7(2):265-273.

161. Alkharfy KM, Frye RF (2007). Effect of Valerian, Valerian/Hops Extracts, and Valerenic Acid on Glucuronidation *In vitro*. *Xenobiotica.* 37(2):113-123.

162. Awad R, Levac D, Cybulska P, Merali Z, Trudeau VL, Arnason JT (2007). Effects of Traditionally Used Anxiolytic Botanicals on Enzymes of the Gamma-Aminobutyric Acid (GABA) System. *Can J Physiol Pharmacol.* 85(9):933-942.

163. Leuschner J, Müller J, Rudmann M (1993). Characterization of the Central nervous Depressant Activity of a Commercially Available Valerian Root Extract. *Arzneimittelforschung.* 43(6):638-641.

164. Eadie MJ. (2004) Could Valerian have been the First Anticonvulsant? *Epilepsia.* 45(11):1338-1343.

165. Rezvani ME, Roohbakhsh A, Allahtavakoli M, Shamsizadeh A (2010). Anticonvulsant Effect of Aqueous Extract of *Valeriana officinalis* in Amygdala-Kindled Rats: Possible Involvement of Adenosine. *J Ethnopharmacol.* 127(2):313-318. Epub 2009 Nov 10.

166. Oliva I, GonzÃ¡lez-Trujano ME, Arrieta J, Enciso-RodrÃguez R, Navarrete A (2004). Neuropharmacological Profile of Hydroalcohol Extract of *Valeriana edulis* ssp. procera Roots in Mice. *Phytother Res.* 18(4):290-296.

167. Gilani AH, Khan AU, Jabeen Q, Subhan F, Ghafar R (2005). Antispasmodic and Blood Pressure Lowering Effects of *Valeriana wallichii* are Mediated through K+ Channel Activation. *J Ethnopharmacol.* 100(3):347-352.

168. Krystal AD, Ressler I (2001). The Use of Valerian in Neuropsychiatry. *CNS Spectr.* 2001 Oct;6(10):841-847.

169. Hazelhoff B, MalingrÃ© TM, Meijer DK (1982). Antispasmodic Effects of *Valeriana* compounds: an *In-vivo* and *In-vitro* Study on the Guinea-Pig Ileum. *Arch Int Pharmacodyn Ther*. 257(2):274-287.

170. Chaplin RL Jr, Jedynak J, Johnson D, Heiter D, Shovelton L, Garrett N (2007). The Effects of Valerian on the Time Course of Emergence from General Anesthesia in Sprague-Dawley Rats *(Rattus norvegicus). AANA J.* 75(6):431-435.

171. Yuan CS, Mehendale S, Xiao Y, Aung HH, Xie JT, Ang-Lee MK (2004). The Gamma-Aminobutyric Acidergic Effects of Valerian and Valerenic Acid on Rat Brainstem Neuronal Activity. *Anesth Analg.* 98(2):353-358

172. De Feo V, Faro C (2003). Pharmacological Effects of Extracts from *Valeriana adscendens* Trel. II. Effects on GABA Uptake and Amino Acids. *Phytother Res.* 17(6):661-664.

173. Circosta C, De Pasquale R, Samperi S, Pino A, Occhiuto F (2007). Biological and Analytical Characterization of Two Extracts from *Valeriana officinalis. J Ethnopharmacol*. 112(2):361-367. Epub 2007 Mar 20.

174. Fields AM, Richards TA, Felton JA, Felton SK, Bayer EZ, Ibrahim IN, Kaye AD (2003). Analysis of Responses to Valerian Root Extract in the Feline Pulmonary Vascular Bed. *J Altern Complement Med.* 9(6):909-918

175. Fachinetto R, Villarinho JG, Wagner C, Pereira RP, Avila DS, Burger ME, Calixto JB, Rocha JB, Ferreira J (2007). *Valeriana officinalis* does not Alter the Orofacial Dyskinesia Induced by Haloperidol in Rats: Role of Dopamine Transporter. *Prog Neuropsychopharmacol Biol Psychiatry.* 31(7):1478-1486. Epub 2007 Jul 4.

176. Neill M, Dixon PS (2007). Effects of a Preincisional 14-day Course of Valerian on Natural Killer Cell Activity in Sprague-Dawley Male Rats Undergoing Abdominal Surgery. *Holist Nurs Pract.* 21(4):187-193.

177. Rehni AK, Pantlya HS, Shri R, Singh M (2007). Effect of Chlorophyll and Aqueous Extracts of *Bacopa monniera* and *Valeriana wallichii* on Ischaemia and Reperfusion-Induced Cerebral Injury in Mice. *Indian J Exp Biol.* 45(9):764-769.

178. Dimpfel W, BrattstrÃ¶m A, Koetter U (2006). Central Action of a Fixed Valerian-Hops Extract Combination (Ze 91019) in Freely Moving Rats. *Eur J Med Res*. 11(11):496-500.

179. Muller CE (2001). A1 adenosine receptors and their ligands: overview and recent developments. *Farmaco.* 56(1-2):77-80.

180. BrattstrÃ¶m A (2007). Scientific Evidence for a Fixed Extract Combination (Ze 91019) from Valerian and Hops Traditionally Used as a Sleep-Inducing Aid. *Wien Med Wochenschr.* 157(13-14):367-370.

181. Vissiennon Z, Sichardt K, Koetter U, BrattstrÃ¶m A, Nieber K (2006). Valerian Extract Ze 911 Inhibits Postsynaptic Potentials by Activation of Adenosine A1 Receptors in Rat Cortical Neurons. *Planta Med.* 72(7):579-583. Epub 2006 Apr 28.

182. Abourashed EA, Koetter U, Brattström A (2004). *In vitro* Binding Experiments with a Valerian, Hops and their Fixed Combination Extract (Ze91019) to Selected Central Nervous System Receptors. *Phytomedicine.* 11(7-8):633-638.

183. Lacher SK, Mayer R, Sichardt K, Nieber K, MÃ¼ller CE (2007). Interaction of Valerian Extracts of Different Polarity with Adenosine Receptors: Identification of Isovaltrate as an Inverse Agonist at A1 Receptors. *Biochem Pharmacol.* 73(2):248-258. Epub 2006 Oct 6.

184. Sichardt K, Vissiennon Z, Koetter U, BrattstrÃ¶m A, Nieber K (2007). Modulation of Postsynaptic Potentials in Rat Cortical Neurons by Valerian Extracts Macerated with Different Alcohols: Involvement of Adenosine A(1)- and GABA(A)-Receptors. *Phytother Res.* 21(10):932-937.

185. Gramowski A, JÃ¼gelt K, StÃ¼we S, Schulze R, McGregor GP, Wartenberg-Demand A, Loock J, SchrÃ¶der O, Weiss DG (2006). Functional Screening of Traditional Antidepressants with Primary Cortical Neuronal Networks Grown on Multielectrode Neurochips. *Eur J Neurosci.* 24(2):455-465.

186. Sharifzadeh M, Hadjiakhoondi A, Khanavi M, Susanabadi M (2006). Effects of Aqueous, Methanolic and Chloroform Extracts of Rhizome and Aerial Parts of *Valeriana officinalis* L. on Naloxone-Induced Jumping in Morphine-Dependent Mice. *Addict Biol.* 11(2):145-151.

187. Si XY, Jia RH, Huang CX, Ding GH, Liu HY (2003). [Effects of *Valeriana officinalis* var. *latifolia* on Expression of Transforming Growth Factor *beta* 1 in Hypercholesterolemic Rats]. [Article in Chinese] *Zhongguo Zhong Yao Za Zhi. =China J Chin mater med.* 28(9):845-848

188. Yaniv R, Segal E, Trau H, Auslander S, Perel A (1995). Natural Premedication for Mast Cell Proliferative Disorders. *J Ethnopharmacol.* 46(1):71-72.

189. Davydov BI, Ushakov IB, Razgovorov BL (1985). [Behavior of Cats Following Gamma-Irradiation of the Head: the Induced Pleasure Test]. [Article in Russian] *Radiobiologiia.* 25(1):116-119.

190. Malva JO, Santos S, Macedo T (2004). Neuroprotective Properties of *Valeriana officinalis* extracts. *Neurotox Res*. 6(2):131-140.

191. EbringerovÃ¡ A, KardosovÃ¡ A, HromÃ¡dkovÃ¡ Z, HrÃ-balovÃ¡ V (2003). Mitogenic and Comitogenic Activities of Polysaccharides from Some European Herbaceous Plants. *Fitoterapia.* 74(1-2):52-61.

192. Narimanov AA, Gavriliuk BK (1989). [The Synergism of the Action of Gamma Radiation and Cardiovascular Preparations on Lymphoid Cells in Culture]. [Article in Russian] *Radiobiologiia.* 29(2):188-191.

193. de Oliveria DM, Barreto G, De Andrade DV, Saraceno E, Aon-Bertolino L, Capani F, Dos Santos El BachÃ¡ R, Giraldez LD (2009). Cytoprotective Effect of *Valeriana officinalis* Extract on an *In vitro* Experimental Model of Parkinson Disease. *Neurochem Res.* 34(2):215-220. Epub 2008 May 30.

194. Jacobo-Herrera NJ, Vartiainen N, Bremner P, Gibbons S, Koistinaho J, Heinrich M (2006). NF-*Kappa* B Modulators from *Valeriana officinalis. Phytother Res.* 20(10):917-919.

195. Letchamo W, Ward W, Heard B, Heard D (2004) Essential Oil of *Valeriana officinalis* L. Cultivars and their Antimicrobial Activity as Influenced by Harvesting Time under Commercial Organic Cultivation. *J Agric Food Chem.* 52(12):3915-3919.

196. Shalini, Srivastava R (2008). Antifungal Activity Screening and HPLC Analysis of Crude Extract from *Tectona grandis, Shilajit, Valeriana wallachi. The Int J of Alter Med.* 5(2)

197. Lazar-Baker EE, Hetherington SD, Ku VV, Newman SM (2011). Evaluation of Commercial Essential oil Samples on the Growth of Postharvest Pathogen *Monilinia fructicola* (G. Winter) Honey. *Lett Appl Microbiol.* 52(3):227-232. doi: 10.1111/j.1472-765X.2010.02996.x.

198. Berdonces JL (2001). [Attention Deficit and Infantile Hyperactivity]. [Article in Spanish] *Rev Enferm.* 24(1):11-14.

199. Kim J, Seo SM, Lee SG, Shin SC, Park IK (2008). Nematicidal Activity of Plant Essential Oils and Components from Coriander *(Coriandrum sativum)*, Oriental Sweetgum *(Liquidambar orientalis)*, and Valerian *(Valeriana wallichii)* Essential Oils Against Pine Wood Nematode *(Bursaphelenchus xylophilus)*. *J Agric Food Chem.* 56(16):7316-7320. Epub 2008 Jul 8.

200. Tufik, S, Fuhita K, Seabra MDL, Lobo LL (1996). Effects of a Prolonged Administration of Valepotriates in Rats on the Mothers and Their Offspring. *J. Ethnoparmacol.* 41(1-2):39-44.

201. Spinella M (2001). Herbal Medicines and Epilepsy: The Potential for Benefit and Adverse Effects. *Epilepsy Behav.* 2(6):524-532.

202. Ang-Lee MK, Moss J, Yuan CS (2001). Herbal Medicines and Perioperative Care. *JAMA.* 286(2):208-216.

203. Muller SF, Klement S. (2006) A Combination of Valerian and Lemon Balm is Effective in the Treatment of Restlessness and Dyssomnia in Children. *Phytomedicine.* (6):383-387. Epub

204. Baillard C, Bianchi A, Gehan G, Sitbon P, Denantes C, Benhamou D, Cupa M, Samama CM (2007). [Anaesthetic Preoperative Assessment of Chronic Medications and Herbal Medicine Use: a Multicenter Survey]. [Article in French] *Ann Fr Anesth Reanim.* 26(2):132-135.

205. Kleinschmidt S, Rump G, Kotter J (2007). [Herbal Medications. Possible Importance for Anaesthesia and Intensive Care Medicine]. [Article in German] *Anaesthesist.* 56(12):1257-1266.

206. Trapskin P, Smith KM (2004). Herbal Medications in the Perioperative Orthopedic Surgery Patient. *Orthopedics.* 27(8):819-822.

207. Mkrtchyan A, Panosyan V, Panossian A, Wikman G, Wagner H (2005). A Phase I Clinical Study of *Andrographis paniculata* Fixed Combination Kan Jang versus Ginseng and Valerian on the Semen Quality of Healthy Male Subjects. *Phytomedicine.* 12(6-7):403-409.

208. Sun J (2003). Morning/Evening Menopausal Formula Relieves Menopausal Symptoms: a Pilot Study. *J Altern Complement Med.* 9(3):403-409.

209. Zaffani S, Cuzzolin L, Benoni G (2006). Herbal Products: Behaviors and Beliefs Among Italian Women. *Pharmacoepidemiol Drug Saf.* 15(5):354-359.

210. Larimore WL, O'MathÃºna DP (2004). Herbal Products Should be Regulated for Quality Control. *Am Fam Physician.* 69(3):493-494.

211. Dennehy CE, Tsourounis C, Horn AJ (2005). Dietary Supplement-Related Adverse Events Reported to the California Poison Control System. *Am J Health Syst Pharm.* 62(14):1476-1482.

212. Cohen DL, Del Toro Y (2008). A Case of Valerian-Associated Hepatotoxicity. *J Clin Gastroenterol.* 42(8):961-962.

213. Shepherd C (1993). Sleep Disorders. Liver Damage Warning with Insomnia Remedy. *BMJ.* 306(6890):1477.

214. Stasio MJ, Curry K, Sutton-Skinner KM, Glassman DM (2008). Over-the-Counter Medication and Herbal or Dietary Supplement Use in College: Dose Frequency and Relationship to Self-Reported Distress. *J Am Coll Health.* 56(5):535-547.

215. Barreales M, Pérez-Carreras M, Meizoso T, Garrido M, Masedo A, Colina F, Solís JA (2006). [Epstein-Barr Virus Infection and Acute Cholestatic Hepatitis]. [Article in Spanish] *An Med Interna.* 23(10):483-486.

216. Malekzadeh F, Rose C, Ingvar C, JernstrÃ¶m H (2005). [Natural Remedies and Hormone Preparations--Potential Risk for Breast Cancer Patients. A Study Surveys the Use of Agents which Possibly Counteract with the Treatment]. [Article in Swedish] *Lakartidningen.* 102(44):3226-3228, 3230-3231.

217. Chen D, Klesmer J, Giovanniello A, Katz J (2002). Mental Status Changes in an Alcohol Abuser Taking Valerian and Gingko Biloba. *Am J Addict.* 11(1):75-77.

218. Tesch BJ (2002). Herbs Commonly Used by Women: an Evidence-Based Review. *Dis Mon.* 48(10):671-696.

219. Petry JJ, Hadley SK (2001). Medicinal Herbs: Answers and Advice, Part 1. *Hosp Pract* (Minneap). 36(7):57-60.

220. Saeed SA, Bloch RM, Antonacci DJ (2007). Herbal and Dietary Supplements for Treatment of Anxiety Disorders. *Am Fam Physician.* 76(4):549-556.

221. Yao M, Ritchie HE, Brown-Woodman PD (2007). A Developmental Toxicity-Screening Test of Valerian. *J Ethnopharmacol.* 113(2):204-209. Epub 2007 Jun 2.

222. Romero-Jiménez M, Campos-Sánchez J, Analla M, Muñoz-Serrano A, Alonso-Moraga A (2005). Genotoxicity and Anti-Genotoxicity of some Traditional Medicinal Herbs. *Mutat Res.* 585(1-2):147-155.

223. Al-Majed AA, Al-Yahya AA, Al-Bekairi AM, Al-Shabanah OA, Qureshi S (2006). Studies on the Cytological and Biochemical Effects of Valerian in Somatic and Germ Cells of Swiss Albino Mice. *Food Chem Toxicol.* 44(11):1830-1837. Epub 2006 Jun 28.

224. Skórska C, Sitkowska J, Krysińska-Traczyk E, Cholewa G, Dutkiewicz J (2005). Exposure to Airborne Microorganisms, Dust and Endotoxin during Processing of Valerian Roots on Farms. *Ann Agric Environ Med.* 12(1):119-126.

225. Holzgrabe U (2004). [A Riddle Solved--Why Valerian-Hops Extract makes you Drowsy]. [Article in German] *Pharm Unserer Zeit.* 2004;33(5):348.

226. Vo LT, Chan D, King RG (2003). Investigation of the Effects of Peppermint Oil and Valerian on Rat Liver and Cultured Human Liver Cells. *Clin Exp Pharmacol Physiol.* 30(10):799-804.

227. Boniel T, Dannon P (2001). [The Safety of Herbal Medicines in the Psychiatric Practice]. [Article in Hebrew] *Harefuah*. 140(8):780-783, 805.

228. Chan TY, Tang CH, Critchley JA (1995). Poisoning due to an Over-the-Counter Hypnotic, Sleep-Qik (Hyoscine, Cyproheptadine, Valerian). *Postgrad Med J.* 71(834):227-228.

229. Willey LB, Mady SP, Cobaugh DJ, Wax PM (1995). Valerian Overdose: a Case Report. *Vet Hum Toxicol.* 37(4):364-365.

230. von der Hude W, Scheutwinkel-Reich M, Braun R (1986). Bacterial mutagenicity of the tranquilizing constituents of Valerianaceae roots. *Mutat Res.* 169(1-2):23-27.

231. Hui-lian W, Dong-fang Z, Zhao-feng L, Yang L, Qian-rong L, Yu-zhen W (2003). *In vitro* Study on the Genotoxicity of Dichloromethane Extracts of Valerian (DEV) in Human Endothelial ECV304 Cells and the Effect of Vitamins E and C in Attenuating the DEV-Induced DNA Damages. *Toxicol Appl Pharmacol.* 188(1):36-41.

232. www.gaiaprofessional.com

233. Schulz V, Hänsel R, Tyler VE (1998). Rational Phytotherapy: a Physician's Guide to Herbal Medicine. Berlin: *Springer,* 81.

234. Dalla Corte CL, Fachinetto R, Colle D, Pereira RP, Avila DS, Villarinho JG, Wagner C, Pereira ME, Nogueira CW, Soares FA, Rocha JB (2008). Potentially Adverse Interactions Between Haloperidol and Valerian. *Food Chem Toxicol.* 46(7):2369-2375. Epub 2008 Mar 28.

235. Ugalde M, Reza V, GonzÃ¡lez-Trujano ME, Avula B, Khan IA, Navarrete A (2005). Isobolographic Analysis of the Sedative Interaction Between Six Central Nervous System Depressant Drugs and *Valeriana edulis* Hydroalcoholic Extract in Mice. *J Pharm Pharmacol.* 57(5):631-639.

236. Kalus P, Strik WK (2002). [Phytotherapeutic Drugs in Psychiatry]. [Article in German] *Ther Umsch.* 59(6):307-312.

237. Hellum BH, Nilsen OG (2008). *In vitro* Inhibition of CYP3A4 Metabolism and P-Glycoprotein-Mediated Transport by Trade Herbal Products. *Basic Clin Pharmacol Toxicol.* 102(5):466-475. Epub 2008 Mar 6.

238. Hellum BH, Hu Z, Nilsen OG (2007). The Induction of CYP1A2, CYP2D6 and CYP3A4 by Six Trade Herbal Products in Cultured Primary Human Hepatocytes. *Basic Clin Pharmacol Toxicol.* 100(1):23-30.

239. Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Khan IA, Shah A (2005). *In vivo* Effects of Goldenseal, Kava Kava, Black Cohosh, and Valerian on Human Cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. *Clin Pharmacol Ther.* 77(5):415-426.

240. Sood A, Sood R, Brinker FJ, Mann R, Loehrer LL, Wahner-Roedler DL (2008). Potential for Interactions between Dietary Supplements and Prescription Medications. *Am J Med.* 121(3):207-211.

241. Kistorp TK, Laursen SB (2002). [Herbal Medicines--Evidence and Drug Interactions in Clinical Practice]. [Article in Danish] *Ugeskr Laeger.* 164(36):4161-4165.

242. Spinella M. (2002) The Importance of Pharmacological Synergy in Psychoactive Herbal Medicines. *Altern Med Rev.* 7(2):130-137.

243. Williamson EM (2001). Synergy and Other Interactions in Phytomedicines. *Phytomedicine.* 2001 Sep;8(5):401-409.

244. Komori T, Matsumoto T, Motomura E, Shiroyama T (2006). The Sleep-Enhancing Effect of Valerian Inhalation and Sleep-Shortening Effect of Lemon Inhalation. *Chem Senses.* 31(8):731-737. Epub 2006 Jul 20.

245. Ortiz JG, Rassi N, Maldonado PM, González-Cabrera S, Ramos I (2006). Commercial Valerian Interactions with [3H]Flunitrazepam and [3H]MK-801 Binding to Rat Synaptic Membranes. *Phytother Res.* 20(9):794-798.

246. Gold JL, Laxer DA, Dergal JM, LanctÃ´t KL, Rochon PA (2001). Herbal-Drug Therapy Interactions: a Focus on Dementia. *Curr Opin Clin Nutr Metab Care*. 4(1):29-34.

247. GÃ¼zelcan Y, Scholte WF, Assies J, Becker HE (2001). [Mania During the Use of a Combination Preparation with St. John's Wort *(Hypericum perforatum)*]. [Article in Dutch] *Ned Tijdschr Geneeskd.* 145(40):1943-1945.

248. TÃ¯movÃ¡ L (2000). [Interactions Between Herbal Medicines and Drugs]. [Article in Czech] *Ceska Slov Farm.* 49(4):162-167.

249. http://www.nlm.nih.gov/medlineplus/druginfo/natural/870.html

250. Assemi M (2001). Herbs Affecting the Central Nervous System: Gingko, Kava, St. John's Wort, and Valerian. *Clin Obstet Gynecol.* 44(4):824-835.

251. Meolie AL, Rosen C, Kristo D, Kohrman M, Gooneratne N, Aguillard RN, Fayle R, Troell R, Townsend D, Claman D, Hoban T, Mahowald M (2005). Oral Nonprescription Treatment for Insomnia: an Evaluation of Products with Limited Evidence. Clinical Practice Review Committee; American Academy of Sleep Medicine. *J Clin Sleep Med.* 1(2):173-187.

252. Beaubrun G, Gray GE (2000) A Review of Herbal Medicines for Psychiatric Disorders. *Psychiatr Serv.* 51(9):1130-1134.

Dual 5α-Reductase Inhibitor for a Potent & More Comprehensive BPH Management

- The first & the only available dual 5ARI provides rapid, potent and consistent suppression of DHT, which is maintained at 4 years.[1,2,3]
- Provides rapid improvement as early as 1 month in various measures, including prostatic volume and urinary flow.[2]
- Provides a sustained reduction in prostate volume and symptom improvement over 4 years.[3,4]
- Reduces the risk of AUR and BPH-related surgery by 57% and 48%, respectively, at 2 years.[2] The reduction was durable over 4-year treatment.[1]
- Avodart™ is well tolerated[1,2,3]

Avodart™ 適尿通™
Dutasteride

References:

1. Djavan B, Milani S and Fong YK. Dutasteride: a novel dual inhibitor of 5α-reductase for benign prostatic hyperplasia. Expert Opin. Pharmacother. 2005; 6(2): 311-317 **2.** Roehrborn CG, Boyle P, Nickel JC, et al. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types I and II (Dutasteride) in men with benign prostatic hyperplasia. Urology 2002; 60(3): 434-441 **3.** Debruyne F, Barkin J, van Erps P, et al. Efficacy and Safety of Long-Term Treatment with the Dual 5 Alpha-Reductase Inhibitor Dutasteride in Men with Symptomatic Benign Prostatic Hyperplasia. European Urology 2004; 46:488-495 **4.** Roehrborn CG, Lukkarinen O, Mark S, et al. Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5α-reductase inhibitor dutasteride: results of 4-year studies. BJU International 2005; 96:572-577

AVODART™ (Dutasteride) abridged prescribing information

Indications Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH). Reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH. **Dosage and Administration** *Adults (including elderly):* The recommended dose of AVODART is one capsule (0.5 mg) taken orally once a day. The capsules should be swallowed whole and may be taken with or without food. Although an improvement may be observed at an early stage, it can take up to 6 months before a response to the treatment can be achieved. No dose adjustment is necessary in the elderly. *Renal impairment:* The effect of renal impairment on dutasteride pharmacokinetics has not been studied. No adjustment in dosage is anticipated for patients with renal impairment. *Hepatic impairment:* The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. **Contraindications** Patients with known hypersensitivity to dutasteride, other 5 alpha reductase inhibitors, or any component of the preparation; women and children. **Warnings and Precautions** Dutasteride is absorbed through the skin, therefore women and children must avoid contact with leaking capsules. If contact is made with leaking capsules the contact area should be washed immediately with soap and water. The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized and has a half-life of three to five weeks, caution should be used in the administration of dutasteride to patients with liver disease. Digital rectal examination, as well as other evaluations for prostate cancer, should be performed on patients with BPH prior to initiating therapy with dutasteride and periodically thereafter. Serum prostate-specific antigen (PSA) concentration is an important component of the screening process to detect prostate cancer. Generally, a serum PSA concentration greater than 4 ng/mL (Hybritech) requires further evaluation and consideration of prostate biopsy. Physicians should be aware that a baseline PSA less than 4 ng/mL in patients taking dutasteride does not exclude a diagnosis of prostate cancer. Dutasteride causes a decrease in serum PSA levels by approximately 50% after six months in patients with BPH, even in the presence of prostate cancer. Although there may be individual variation, the reduction in PSA by approximately 50% is predictable as it was observed over the entire range of baseline PSA values (1.5 to 10 ng/mL). Therefore to interpret an isolated PSA value in a man treated with dutasteride for six months or longer, PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity and specificity of the PSA assay and maintains its ability to detect prostate cancer. Any sustained increases in PSA levels while on dutasteride should be carefully evaluated, including consideration of non compliance to therapy with dutasteride. Total serum PSA levels return to baseline within 6 months of discontinuing treatment. The ratio of free to total PSA remains constant even under the influence of dutasteride. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing dutasteride therapy, no adjustment to its value is necessary. **Pregnancy and Lactation** The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in normal volunteers aged 18 to 52 (n=27 dutasteride, n=23 placebo) throughout 52 weeks of treatment and 24 weeks of post treatment follow-up. At 52 weeks, the mean percent reduction from baseline in total sperm count, semen volume, and sperm motility were 23%, 26%, and 18%, respectively, in the dutasteride group when adjusted for changes from baseline in the placebo group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of follow-up, the mean percent change in total sperm count in the dutasteride group remained 23% lower than baseline. While mean values for all semen parameters at all time points remained within the normal ranges and did not meet predefined criteria for a clinically significant change (30%), two subjects in the dutasteride group had decreases in sperm count of greater than 90% from baseline at 52 weeks, with partial recovery at the 24-week follow-up. The clinical significance of dutasteride's effect on semen characteristics for an individual patient's fertility is not known. Dutasteride is contraindicated for use by women. Dutasteride has not been studied in women because pre clinical data suggests that the suppression of circulating levels of dihydrotestosterone may inhibit the development of the external genital organs in a male foetus carried by a woman exposed to dutasteride. It is not known whether dutasteride is excreted in breast milk. **Adverse Reactions** *Clinical Trial Data:* The following investigator-judged drug-related adverse events (with incidence more than or equal to 1%) have been reported more commonly in the three phase III placebo controlled studies on dutasteride treatment compared to placebo:

Adverse event	Incidence during year 1 of treatment		Incidence during year 2 of treatment	
	Placebo (n= 2158)	Dutasteride (n= 2167)	Placebo (n= 1736)	Dutasteride (n= 1744)
Impotence	3%	6%	1%	2%
Altered (decreased) libido	2%	4%	<1%	<1%
Ejaculation disorders	<1%	2%	<1%	<1%
Breast disorders +	<1%	1%	<1%	1%

+ includes breast tenderness and breast enlargement

No change to the adverse event profile was apparent over a further 2 years in open label extension studies.

Postmarketing Data: Allergic reactions, including rash, pruritus, urticaria, localised oedema and angioedema. **Overdosage** There is no specific antidote for dutasteride, therefore in cases of suspected overdosage, symptomatic and supportive treatment should be given as appropriate.

Please refer to the AVODART full prescribing information for warnings, precautions, interactions, pregnancy, lactation, adverse reactions and overdose.

Abridged PI (GDS 07)

Full prescribing information is available upon request. Please read the full prescribing information.

N09AAD07803062009

GlaxoSmithKline

GlaxoSmithKline Limited
23/F., Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong Tel: (852) 3189 8989 Fax: (852) 2506 1378

Students' Experience on Attending the Forbidden City Conference in Beijing

CHAN, Wing Fat[a]; CHAU, Marco[b]; HO, Jason[a]; HO, Sam Ka Ming[a]; KONG, Sarah Hiu Hung[b]; LAU, Kai Yeung[b]; LI, Joey Wing Yi[b]; NG, Freddie Ting Fat[b]; TAI, Amy Yan Yee[b]

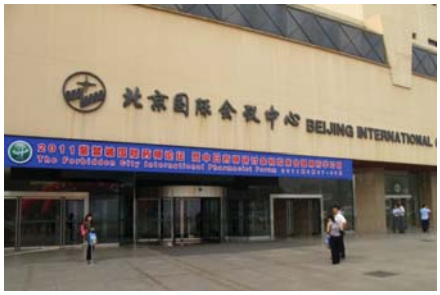
[a] *School of Pharmacy, The Chinese University of Hong Kong, Shatin, NT, Hong Kong*

[b] *Department of Pharmacy & Pharmacology, University of Hong Kong, Pokfulam, Hong Kong*

Pharmacy students have always been looking closely at the development of the pharmaceutical industry in Hong Kong and the world. To reconsolidate and further our understandings of the industry in China, we, a group of pharmacy students in Hong Kong, attended "The Forbidden City International Pharmacist Forum 2011" held in Beijing in May. Availing ourselves of this invaluable opportunity, we would like to shed light on our experience obtained and lessons learnt amid the Conference.

The student contingent is jetset and ready to embark on the journey up north

Structure and organisation of the Forum



A first glimpse of the site of The Forbidden City International Pharmacist Forum, held at the Beijing International Convention Centre

The 2011 Forbidden City International Pharmacist Forum lasted from 27 May to 31 May. This year, its aim was 'the safe and rational uses of drugs'. It commenced with an opening ceremony. Pharmacist representatives of each country gathered on the stage. From the number of participants there, we could know the nationality diversity in this Forum.

The exhibition site is a picture of extreme calm moments before the commencement of the Forum

A series of seminars followed the opening ceremony. Pharmacists shared their views on pharmacy education and pharmacy development in their own countries. In particular, the situation in mainland China was the highlight as there will be a large room for pharmacy development in the near future.

The Forum kicks off with the opening speeches by the honorable guests in the main Exhibition Hall, after which participants were free to explore the various exhibits and sessions around the site

At the first night, there was a welcoming dinner, during which we sat with some practicing pharmacists. We talked about our school life and the expectation to the career while practicing pharmacists mostly shared their work experience.

Besides seminars, pharmacy students in the mainland had a speech competition and debate. They fully demonstrated their confidence and competence in these two events. The audience were all impressed by them.

Well rested, everyone looks eager for a second day at the forum

One of the most popular talks was given by Mr Peter Suen, CEO & Chief Pharmacist at ActiveCareMedics (second from left) regarding the Implementation of Professional Medication Management Service in Old Age Homes in Hong Kong, which is why he has no shortage of fans

After staying in the convention hall for three days, we went out for a hospital visit. Our destination was Beijing Hospital. Not only did we visit the out-patient pharmacy, but we also visited the herbal medicine compartment.

Before we headed to the Beijing International Airport for return, we visited Johnson & Johnson Co.. Although we did not see any production line, a lot of information regarding pharmacy development in mainland China was presented to us. We also had a look at the high-technology set up in Johnson & Johnson's office.

Pharmacy undergraduates of HKU and CU together at night for sharing and debrief after the Forum

The 2011 Forbidden City International Pharmacist Forum had been drawn to a full stop. It was our pleasure to participate in this wonderful event. We all look forward to next year's Pharmacist Forum!

Lessons and reflections

The Forbidden City International Pharmacist Forum 2011 in Beijing, China was truly a remarkable experience to be able to visit such a grand-scale forum as a student. Not only was there exposure to the way different countries such as China, Japan, USA run their pharmacies but also it was incredible to be able to visit Beijing's hospital and also Johnson and Johnson Co.'s Headquarters in China.

At the forum, the most interesting talk was the pharmacy system in Japan, its organization and how they use technology to help give pharmaceutical care in private stalls. There was a detailed pamphlet about their computer system used in Japan; unfortunately, it was all in Japanese. Another hot topic presented was on adverse drug reactions with much emphases on where errors easily occur. It is very important to avoid, screen and correct these orders for many patients succumb not to diseases but these mistakes each year. Hopefully in the future with improve technology and the measures already taken as well as to be improved upon, there can be minimal error and next-to-zero deaths. Compared with pharmacists around the globe, Hong Kong still has room for much improvement.

At the first night of the Conference, there was a welcome dinner for all participants. A variety of traditional Beijing food was served. At the same time, there were performances by the pharmacists all around the world, including a number of provinces in China. Quite a lot of the performances were unique and entertaining. For example, some of the pharmacists from China sang "You and Me", the Olympic theme song in 2008; while, a representative from the United States played a guitar solo. We, the students from Hong Kong, sang a song called "The Red Sun", which encourages people not to give up when facing difficulties. During the Conference dinner, we could not only exchange information about pharmacy but also differences in culture and practice. This let us know more about other pharmacists in the globe. All of the participants, including us, enjoyed this meaningful night very much.

Representing Hong Kong, the members of the Pharmaceutical Society of Hong Kong pause for a picture after a performing a soulful rendition of Hacken Lee's Red Day during the Welcoming Dinner

Aspiring pharmacists exchange ideas with two homegrown pharmacists Ritchie and Rico over dinner

In addition, it was very interesting to walk through the bustling Beijing Hospital. To be able to witness both Chinese and Western medications being prescribed and then dispensed, sometimes together to the same patient, is really a crazy thing. There are many drug interactions between the western medications but to include Chinese herbals as well into this kaleidoscope just makes everything dangerously flash red on every turn, albeit the possible additional therapeutic effects exerted by the Chinese medicines. We ponder this might be one of the challenges Hong Kong is facing since our patients might be taking both Western medicines and Chinese ones concurrently. Something different about the medical system in China and that in Hong Kong is that each patient pays for every pill. The hospital can immediately use an MS-MS to identify unknown substances obtained from a patients or any suspicious stock in a laboratory floor.

The third day students were granted the privilege to visit the famous Beijing Hospital, to understand about the China healthcare system as well as the maintenance of a hospital pharmacy

A pharmacist uses a flow chart to explain the distribution and management of drugs within the hospital

Furthermore, a visit to the Johnson and Johnson Co.'s Headquarters in Beijing showed the power of big pharmaceutical corporations. We were introduced to the structure of the company, as well as the possibilities for business relationships between Hong Kong and China. We learned about some of the company's history like how in China it started off as a plant in Xi'an. There are many departments in the company, in which the staff can fully utilize their talents to work in them. Growing up with this company's name having always been stocked all the shelves of many stores, maybe it would be fun to join into the industrial team and not always be just the consumer.

Next up was a visit to renowned pharmaceutical, medical and consumer products manufacturer Xian-Janssen, to which there was a series of special talks regarding clinical trials, product development and marketing strategy at the company. Here, the chairman of PSHK presents the CEO with a thank you gift

Differences between HK and China in terms of pharmacists and the industry

As influenced by traditional way of thinking, most Chinese citizens do not recognize that pharmacists are capable of work besides dispensing. Pharmacists are therefore assigned the work of dispensing in China. This contributes to the development of a system which emphasizes the diagnosis and treatment but not medication. Furthermore, the role of pharmacists is not as essential as it should be under this situation. When compared to China, Hong Kong seems to have similar working environment for pharmacists. Notwithstanding, under the work of senior pharmacists, it is improving in Hong Kong.

Under the system mentioned above, clinical pharmacy is not sophisticated in China. This is also attributable to the law requirement which does not state that pharmacists have the right, the responsibility to propose, to carry out treatment on patient directly to whatever extent. Therefore, not developing clinical pharmacy is not illegal in China. Despite these, the forum stressed the development of clinical pharmacy in China. Things are being done to introduce clinical pharmacy, like training clinical pharmacists, with the situation improving in China. Similarly, in Hong Kong, clinical pharmacy is not widely practiced but is evolving.

Another stark difference derived from the traditional way of thinking of most Chinese is the prevalence of traditional Chinese medicines. Public hospital in China provides traditional Chinese medicines as well as Western medicines. The Chinese medicine pharmacy supplies a large number of traditional herbal medicines, which are more acceptable for the older generation. Such arrangement of the pharmacy could support alternative Chinese medical treatments to people who believe in Chinese medicine. In Hong Kong, there are a number of public hospitals providing traditional Chinese medicines to out patients. However, there is no Traditional Chinese Medicine Hospital in which patients are treated with both western and Chinese medicines. Most patients who wish to receive any Chinese medicine need to seek private Chinese medicine practitioners on their own. There would be a great improvement in the medical care system if the Hong Kong public hospitals could provide Chinese medicine treatment together with western medicines like those in Beijing.

The trip really gives us a chance to know what is going on in China. We used to think that China is not as prosperous as Hong Kong so the development of pharmacy may not be as advanced as that in Hong Kong. However, the trip shows us that Hong Kong does not precede China with a large distance and two places are above the starting point whence a long way is yet to go.

Suggestions concerning further exchange

Pharmaceutical industry and the role of pharmacists in China have been expanding quickly in recent years. Besides, it is doubtless that Hong Kong will have closer interactions with the pharmaceutical industry in China. Exchange between pharmacists from both places is, therefore, a critical and necessary move to further expand the industry as well as the pharmacists' roles.

Before any concrete suggestions, however, basic understanding of the role of pharmacists in China and HK should be well acknowledged by each other. It is possible that pharmacists in Hong Kong are not familiar with the situation in China, and vice versa. From our own experience, it would be quite difficult to understand how a certain local pharmacy-related system works when we only know little about it. To overcome such obstacle, some lectures introducing the healthcare system and the role of pharmacists in China would be justifiable.

As a lesson learnt from this Conference, we think that such academic meeting provides an important bridge for pharmacists from different places to communicate and exchange. Organized every year, Hong Kong Pharmacy Conference could serve this purpose well. In our opinion, an extra 'China Session' may be organized to invite professionals from China to attend with topics focusing on the pharmacy education and pharmaceutical industry in China. They can also attend other sessions to learn more about the pharmacy situation in Hong Kong. During the Conference, pharmacists from China are also welcome to visit public hospitals, community pharmacies and local pharmaceutical companies in Hong Kong to gain better understanding of our local pharmaceutical industry.

It is understandable that it may not be easy to ask so many pharmacists, many of whom hold important roles in hospitals, community pharmacies, et cetera, to attend a conference outside their working regions or provinces for a few days or even a week. In view of this, Internet could be an alternative to enhance exchange between pharmacists from China and Hong Kong. Some online academic forums can be set up, allowing pharmacists in different places in China and Hong Kong to discuss freely on the Internet. At the same time, free access to the local pharmaceutical journals online could be another way to allow a better understanding of the situation of pharmaceutical industry in different parts of China.

It would also be wise to have exchange between pharmacy students from China and Hong Kong, at a time before they become registered pharmacists. We are deeply impressed by the pharmacy students in China who also attended the Conference. They were well-prepared, smart and responding quickly, as we observed from a student debate during the Conference. We think it would be mutually advantageous to organize an informal gathering for pharmacy students from two places to share and learn from one another.

Ways to tackle existing problems in the healthcare systems in HK and China through cooperation

Cooperation is often one of the creeds of advancement. It is our strong conviction that through the collaborations between Hong Kong and China, the healthcare systems of both parties in the field of pharmacy can be bettered so pharmaceutical care of patients can be optimized.

China has always been reputed for its devotion to and leading position in TCM development and research, which is lacking in Hong Kong. If these research data could be made available to Hong Kong, whether through further conference, student exchange, or online data bank as mentioned before, it could promote safer and more prevalent use of the Chinese medicines. This renders patients with a wider spectrum of drugs

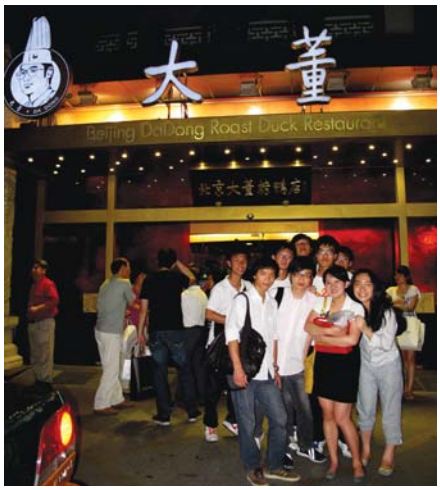
that can be administered in wrestling with a larger variety of diseases, while allows pharmacists and other medical professionals to provide more comprehensive care plans concerning the drug regimens.

Learning from the Conference lectures, China is facing antibiotics abuse, which has battered the efficacy of these medications. In an attempt to help rationalize their uses in the mainland, we could purvey mainland medical authorities with different established protocols of the use of antibiotics such that the healthcare professionals can have clearer guidelines of the domain.

As aforementioned, each patient in China has to pay for his or her own medications. Amid the Conference, we learnt that China is now trying to re-form and expand its primary healthcare system by listing some items that can be provided to the multitude freely. Hence, we think Hong Kong pharmacists could give advice on the reformation with close regards to the drug list which is using in Hong Kong currently. Apart from assisting the growth of pharmaceutical care in China, this could also enhance academic exchange between the two places.

In short, the combination of traditional Chinese medicine and Western medicine has not always worked smoothly in both Hong Kong and China. To tackle this problem, the mainland and Hong Kong can work together to allow knowledge exchange between the two parties so both will be equipped with knowledge of different aspects. Policies or regulations that are adopted in one region can act as references for other regions might be another solution as well.

Concluding our experience obtained in the trip, we sincerely hope that more cooperation between Hong Kong and China can be executed in near future to strengthen the bond between the parties. We truly believe that a closer partnership is a recipe for ameliorations in the healthcare systems of the two places and ultimately benefits our invalids.



No trip to Beijing would be complete without a signature Peking duck at the infamous Da Dong Roast Duck Restaurant


We bid a tearful goodbye to Beijing with expanded horizons and new friends made

The 40th Term Practising Pharmacists Association of Hong Kong (PPAHK) General Council

President:	Ms CHANG Iris
First Vice-President:	Mr LUI Godfrey
Second Vice-President:	Mr CHEUNG Kin Man, Kevin
Honorary Treasurer:	Mr TANG Bernard
Honorary Secretary:	Mr CHAN Lok Hang, Tom

Council Members:	Dr CHUNG Yan
	Mr CHEUNG Foster
	Mr CHAN Jacky
	Mr LEE Gordon
	Mr HO James
	Dr SUNG Christy

The Society of Hospital Pharmacists (SHPHK) General Committee Members 2011-2012:

President:	SO Yiu Wah
Vice President:	CHUI Chun Ming William
Treasurer:	LAI Oi Lun Ellen
Secretary:	NG Long Yee Stephanie

General Committee Members:	CHAN Man Chi Sarah
	CHAN Wing Lam Phoebe
	CHEUNG Ka Lung Kenneth
	CHU Man Wa Amy
	CHUNG Wing Fai Kenneth
	HUI Hoi Yun Helen
	LING Ho Ming Michael
	NG Man Keung
	PANG Ying Ho Bobby
	TONG Pui Kwan Candy
	WONG Sze Ho Johnny

藥物教育講座展覽車 推動藥物教育

從本港公立醫院病人藥物浪費調查中，顯示有近三成受訪病人藥物依從性不佳。 浪費的處方藥物高達16%。有見及此，醫院藥劑師學會 (SHPHK) 首推「藥物教育講座展覽車」爲市民服務。

每年本港有約600萬人次使用公立醫院專科門診服務，當中一些長期病患者，需持續使用醫生處方藥物。香港醫院藥劑師學會關注本港病人服藥依從性問題，於本月中進行一項「本港公立醫院病人服藥依從性調查」，於公立醫院訪問了427名需持續用藥的病人，了解他們的用藥依從性。

「三高」類藥物最常被浪費

調查發現，在受訪的病人中，有27% (117人)曾未有依正確指示服藥，包括忘記服藥、不準時服藥、病情好轉即不依指示服藥或病情惡化即不依指示服藥等。學會發現，這批藥物依從性不佳的病人，平均每人每月浪費的藥物金額為$40.85，相等於浪費了獲處方藥物的16%。

香港醫院藥劑師學會會長蘇曜華與展覽車

醫院藥劑師學會會長蘇曜華表示：「調查發現，三大最常被浪費藥物，均屬『三高』類藥物，包括高血壓(60次)、糖尿病(20次)及高血脂(15次)，至於常見的浪費藥物理由，則包括忘記服藥、對藥物感到混亂、擔心副作用、自感病徵消失毋需用藥、不信任醫生處方及出現副作用等」。結果帶出兩個需要關注的要點：第一，病人藥物依從性不佳，治療效果會受到影響；第二，應透過藥物教育，提升病人服用藥物的依從性，從而減少浪費。

病人個案分享：擅自決定停藥

七十多歲的婆婆因為高血壓而求診，婆婆到達藥劑部取藥時，面上露出不快之情，質問藥劑師為何又是相同藥物，藥劑師於是向她查問過去是否有服用過，婆婆雖表示有，但藥劑師懷疑婆婆並沒有服用。在藥劑師再三誘導下，婆婆才和盤托出；原來她曾在用藥後出現面紅耳赤、心跳加快等情況，於是一直以來均無依時服藥，只會在血壓非常高時才服用藥物。而經藥劑師解釋下，病人明白相關藥物的副作用會在服藥一段期間後適應，而且若自行停藥，對健康有害無益，最終她亦能適當用藥。

另一名中年糖尿病女病人，需要服用血壓藥，但服用過後常出現乾咳情況，因而自行停藥，因為她自覺其血壓145/90mmHg並非太差。直至有一次覆診，她從藥物資訊站找到有關此血壓藥的資料，才發現乾咳乃此藥常見的副作用，其後她詢問藥劑師的意見，藥劑師着她告訴醫生實際情況，醫生其後處方另一類降血壓藥給她。

本港首架藥物教育講座展覽車啟動　提供免費檢測

為促進本港的藥物教育，提升病人服藥的依從性，學會策動了「藥物教育講座展覽車」計劃，並於2011年四月中旬開始正式啟動。藥物教育講座展覽車將展開為期四個月的推廣活動，為市民提供正確藥物資訊和教育，當中針對三高(高血壓、高血糖及高膽固醇)及骨質疏鬆等問題，期間亦會向市民提供免費檢測。

活動期間，藥物教育資訊車將每日停泊在全港不同地點，車上會展示最新藥物治療資訊，播放錄像，亦有工作人員在旁講解，協助市民容易理解。此外，在週六及周日，車上會提供指定的健康測試，暫定四月及五月份安排血糖和血脂測試，六月及七月份安排骨質密度測試等。

藥物教育講座展覽車的外觀。你有在街上見過嗎?

車內有很多藥物教育資訊

展覽車服務地點

領匯屋邨 / 商場 (20日)：
華富邨、龍翔、樂富、禾輋邨、厚德邨、何文田廣場、慈雲山中心、麗晶花園、小西灣邨、龍蟠苑、彩虹邨、屯門、元朗、將軍澳、馬鞍山、沙田、大埔

私人屋苑 (20日)：
太古城、杏花邨、香港仔中心、海怡半島、和富中心、城市花園、美孚新邨、奧海城、屯門市廣場、新港城、新都城、黃埔花園、沙田第一城、沙田大會堂、元朗

此項藥物教育活動的經費由美國默沙東藥廠有限公司(MSD)贊助。

Active ingredients:
Japanese encephalitis vaccine (inactivated, adsorbed)

Presentations:
IXIARO is a white and slightly milky suspension for injection (0.5ml in a glass syringe with or without a separate needle, pack size of 1) and will become homogenous upon shaking

Indications:
IXIARO is a vaccine against Japanese encephalitis virus. It is used to prevent infection with the Japanese encephalitis virus (JEV). This virus is mainly found in Asia and is transmitted to humans by mosquitoes that have bitten an infected animal (like pigs).

Many infected people develop may develop mild symptoms. In people who develop severe disease, JE usually starts as a flu-like illness, with fever, chills, tiredness, headache, nausea and vomiting. Confusion and agitation also occur in the early stage.

Dosage and Administration
IXIARO should be given to adults 18 years or over:

You will receive two injections:

- First injection on day 0
- Second injection 28 days after the first injection

Make sure you finish the complete vaccination course of two injections, the second injection should be given at least 1 week before you will be at risk of exposure to JE virus. Otherwise, you may not be fully protected against the disease.

A booster third dose should be given within the second year i.e. 12-24 months after the recommended primary immunization, prior to potential re-exposure to JEV. Persons at continuous risk for acquiring Japanese encephalitis should receive a booster dose at month 12 after primary immunization.

IXAIRO is injected into your upper arm muscle, it is not to be injected into the blood vessels. If you miss a scheduled injection, arrange a second injection as you will not be fully protected. There is data that the second injection can be given up to 11 months after the first one.

Contraindications
- Allergic to the active substance or any other ingredients
- Signs of allergic reaction includes itchy rash, shortness of breathe and swelling of face and tongue
- High fever

Precautions
- Bleeding disorder
- Immunodeficiency
- Should be avoided for use in Pregnancy
- Breast feeding should be avoided

Possible Side Effects
Headache, muscle pain, tiredness, injection site reactions (pain & tenderness, itching, redness and swelling), fatigue, nausea, flu like illness, fever, vomiting, skin rash, vertigo, dizziness, diarrhoea, musculoskeletal stiffness etc.

Storage Conditions
Should be stored between 2-8 degrees in the fridge and away from light

Forensic Classification:
P1S1S3

Hong Kong Pharmaceutical Journal: Detail Instructions for Authors

INTRODUCTION

Hong Kong Pharmaceutical Journal (HKPJ) is the official publication of the Pharmaceutical Society of Hong Kong, the Practising Pharmacists Association of Hong Kong and the Society of Hospital Pharmacists of Hong Kong. It is a journal of the pharmacists, for the pharmacists and by the pharmacists. The Journal is currently divided into several sections: ***Editorial Comment; News & Short Communications; Pharmacy Practice; Over-the-Counter & Health; Drug & Therapeutics; Herbal Medicines & Nutraceuticals; Pharmaceutical Technology*** and ***New Products***. It publishes review articles or original papers relevant to these different fields of pharmacy. In addition to the regular four issues of the Journal per year, there are issues dedicated solely to reports on special function of the society. The Aims and Scope of the Journal are published on the inside back cover of each issue.

Submission of Manuscript

Submission of a paper implies that it has not been published previously, that it is not under consideration for publication elsewhere, and that if accepted it will not be published elsewhere in the same form, in English or in any other language, without the written consent of the publisher. Authors are specifically discouraged from submitting papers as fragmented studies of a particular topic. A manuscript must be indicated which section it is belonged. Upon received, it will be screened by a **Sectional Editor** of HKPJ for initial consideration before it is sent out for further review or comment.

For online submission:
Authors are encouraged to submit manuscripts using the online submission system. Access to the system, and full instructions on its use, can be found on the HKPS website at: http://www.HKPS.org/HKPJ/Guidelines. In creating the electronic version of their manuscript, authors are requested to follow the guidelines for submitting files. The paper should be submitted as a single file, prepared with a standard word-processor such as Microsoft Word, with embedded tables and graphics. Please note that any embedded graphics must also be submitted as separate, original files. The preferred formats for graphics files are tiff or postscript. All correspondence between Editor and author is performed by email. Authors are reminded that the copyright of their article or paper is automatically transferred to HKPJ once it is accepted for publication in the journal.

For hardcopy submission:
Three copies of the manuscript are required on either 8.5"x11" or A4 paper (two copies are used for review purposes and the original is kept on file at the Section Editor). Copies must be produced on a high-quality printer, and originals and copies of all Figures and Schemes must be fully legible. Initially only send hard copies of the paper; when it has been refereed, revised if necessary, and accepted, you will be requested to send a disk containing the final version with the final hard copy to the appropriate Editor. Make sure that the disk and the hard copy match exactly. The revised manuscript must be returned to the Editors within one month, otherwise it may be deemed to be new and subject to further review. When submitting the final version with a disk please label all disks with "HKPJ", your name, software (e.g. word 2000), hardware used (e.g. PC or Macintosh) and file names with the correct extension (e.g. Fig 1.cdx, Table 1-6.xls). Save text on a separate disk from the graphics, include the text and tables in one file, and provide graphics and structures in separate numbered files. Please remember to keep a backup copy of both the electronic files and original manuscript for reference and safety since we cannot accept responsibility for damage or loss of papers. Original manuscripts are discarded three months after publication unless the Publisher is asked to return original material after use.

Suggested Referees

Please submit, with your manuscript, the names and addresses of 2 potential referees. You may also mention persons who you would prefer not to review your paper.

Editorial Authority

The Editors of HKPJ reserve the right to make alterations to manuscripts submitted for publication. Such alterations will be made if manuscripts do not conform with accepted scientific standards or if they contain matter which in the opinion of the Editors is unnecessarily verbose or unclear. Alterations may be queried, but this will inevitably delay publication.

Preparation of manuscript

The manuscript is required to be written in English, with numbered pages, single-spaced, using Arial 9 point font, and in a suitable word-processing format. Each page should have adequate margins (4 cm) and liberal spaces at top and bottom of the manuscript. All textual elements should begin flush left, with the second paragraphs onwards indent, and should use the wrap-around end-of-line feature, i.e. no returns at the end of each line. Place two returns after every element such as title, headings, paragraphs, figure and table call-outs. Most formatting codes will be removed or replaced on processing your article. Please do not use options such as automatic word breaking, justified layout, double columns or automatic paragraph numbering (especially for numbered references). However do use bold face, italic, subscripts, superscripts etc. The Editors reserve the right to adjust style to certain standards of uniformity. If authors are unfamiliar with HKPJ, they should consult a recent copy (or the free online sample copy available from www.HKPS.com/HKPJ) to see the conventions currently followed for guidance in preparing submissions.

The content of manuscripts must be arranged as follows: (1) a Title Page with authors name(s) and address(es); (2) an Abstract, in which contents are briefly stated; (3) a 4 to 6 Key Word Index, (4) Introduction, and (5) the Results and Discussion (preferably combined). Although each section may be separated by headings, they should form one continuous narrative and only include details essential to the arguments presented. If a discussion is separately provided, it should not include a repetition of the results, but only indicate conclusions reached on the basis of them, and those from other referred works; (6) Conclusions or Concluding Remarks; (7) the Experimental should include brief details of the methods used such that a competent researcher in the field may be able to repeat the work; (8) Acknowledgments; (9) References; (10) Legends, Formulae, Tables and Figures.

Title Page and Author Names: Titles must be as brief as possible, consistent with clarity, and should not exceed 10 words in length. Uninformative phrases such as "Chemical examination of", "Studies on", "Survey of", "New", "Novel" etc. will be deleted. If a paper is part of a series, this must not be given in the heading, but referred to in a footnote in the form: *Part 9 in the series "The Role of Pharmacists in Medical Care of Patients" followed by a numbered reference to the previous part. Author names should be typed right underneath the article title. Each author should identify himself or herself with Surname in capital letters, followed by the first name. All names are separated by a semicolon (;). An asterisk should be placed following the name of the author to whom correspondence inquiries should be made. Full postal addresses must be given for all co-authors. Superscript letters; a, b, c should be used to identify authors located at different addresses.

An **Author's background box** at the end of each article is mandatory to include the author's job title and the affiliated institutle or organization. Full details of telephone, fax numbers and e-mail

address should also be indicated for the corresponding authors. No academic or professional membership title is allowed.

ABSTRACT: The abstract should be on a separate page and briefly describe the results obtained and conclusions reached, not the methods used, or speculations on any other matter. They are not expected to be a complete summary but only an outline of the main findings. The abstract should be contained within 250 words and should be readable without reference to the rest of the paper.

Key Words: Authors must give four to six "key words" or phrases, which identify the most important subjects covered by the paper.

INTRODUCTION should give the minimum historical data needed to give appropriate context to the author's investigation and its relationship to other similar research previously or currently being conducted. Only information essential to the arguments should be presented. Much data can be taken for granted or quoted in abbreviated form. Specific term (genus, species, authority) of all experimental works must be given at first mention and preferably be in the form adopted by the International Scientific Community.

RESULTS AND DISCUSSION: These sections should be carefully prepared with discussions of the results being compared with existing and/or previous knowledge within the field. Authors are, however, encouraged to combine the Results and Discussion sections wherever possible.

EXPERIMENTAL: Subsections on the Experimental Procedures should be italicized and inserted as part of the first line of the text to which they apply. HKPJ encourages an extensive use of abbreviations (these are listed at the back of the Instructions to Authors, or the reader is referred to other sources). The Experimental should begin with a subsection entitled General Experimental Procedures. This subsection will typically contain brief details of instruments used, and identification of sources of specialized chemicals, biochemicals and molecular biology kits. The next subsection describes the source(s) and documentation of biological materials used, whether in reference to whole plants or parts there from, crude drugs, or any other plant material from which identifiable chemical substances are obtained for the first time. Documentation must also include a reference to voucher specimen(s) and voucher number(s) of the compounds, plants or other material examined. If available, authors should quote the name and address of the authority who identified each sample investigated. Specimens should preferentially be deposited in a major regional herbarium where the collection is maintained by state or private institution and which permits loan of such materials. With other microorganisms, the culture collection from which they were either accessed and/or deposited should be included, together with identification of the strain designation code. The Experimental Procedures employed should be concise but sufficiently detailed that a qualified researcher will be able to repeat the studies undertaken, and these should emphasize either truly new procedures or essential modifications of existing procedures. Experimental details normally omitted include: (I) method of preparation of common chemical and biochemical derivatives, (2) excessive details of separation of compounds, proteins and enzymes, e.g. preparation of columns, TLC plates, column and fraction size. Compound Characterization: Physical and spectroscopic data for new compounds must be comprehensive, and follow the order shown below: compound name (and assigned number in text); physical state of compound (e.g. oil, crystal, liquid, etc.), melting and/or boiling point; optical rotation and/or circular dichroism measurements, if optically active; UV; JR, lH NMR; 13C NMR; MS. For all new compounds, either high-resolution mass spectral or elemental analysis data is required. See later section for method of data presentation.

Nomenclature: Chemical nomenclature, abbreviations and symbols must follow IUPAC rules. Whenever possible, avoid coining new trivial names; every effort should be made to modify an existing name. For example, when a new compound is described, it should be given a full systematic name according to IUPAC nomenclature and this should be cited in the Abstract or in the Experimental section.

ACKNOWLEDGMENTS: This section is used to provide brief credit for scientific and technical assistance, and in recognition of sponsorship through financial support and any other appropriate form of recognition.

References: All publications cited in the text should be presented in a list of references following the text of the manuscript. In the text refer to the author's name (without initials) and year of publication (e.g. "Since Peterson (1993) has shown that ..." or "This is in agreement with results obtained later by Kramer.[4]" For two authors both authors are to be listed, with "and" separating the two authors. For more than two authors, use the first author's surname followed by et al. The list of references should be arranged according to the order of their appearance in the text with no more than three authors listed. If number of authors of a reference exceeds three, "et al" is used followed by year of publication in bracket after the first author. Journal titles should be completely shown followed by the volume, issue number in bracket if included, colon and start – final page number. The manuscript should be carefully checked to ensure that the spelling of authors' names and dates are exactly the same in the text as in the reference list. Some examples of references are shown below:

(1) Cabello-Hurtado F, Durst F, Jorrin JV, Werck-Reichhart D. et al. (1998). Coumarins in Helianthus tuberosus: characterization, induced accumulation and biosynthesis. *Biochemistry,* 49(1):1029-1036.

(2) Mabry T, Markham KR, Thomas MB. (1970). *The Systematic Identification of Flavonoids.* 2nd Ed, pp. 79-105. Springer Verlag, New York.

(3) Harborne JB. (1999). Plant chemical ecology. In: Barton D, Nakanishi K, Meth-Cohn 0, (Eds.), *Comprehensive Natural Products Chemistry,* Vol. 8. pp. 137-196. Pergamon, Oxford.

Preparation of Illustrations: All illustrations should be provided in camera-ready form, suitable for reproduction (which may include reduction) without retouching. Illustrations (figures, tables, etc.) should be prepared for either single or double column format. For online submission illustrations should be included in the manuscript and also be submitted separately as high resolution files. For hardcopy submission illustrations should be submitted on separate pages in camera-ready format with legends on separate pages. Hardcopy illustrations supplied by authors are digitally scanned into the appropriate page and must therefore be of the highest quality. Where possible the original electronic files are used, figures produced by computer must therefore be prepared at a minimum resolution of 300 dpi. Refer to all photographs, charts and diagrams as "Figure(s)" and number them consecutively in the order to which they are referred. They should accompany the manuscript, but should not be included within the text. All illustrations should be clearly marked with the figure number and the author's name (either on the back if submitting on paper or with a clear file name if submitting online). All figures are to have a caption, which should be supplied on a separate page. Note: Illustrations of the following type generally will not be accepted for publication: (1) diagrams or photographs of chromatograms (PC and TLC), electrophoretic separations, or recorder traces of GC and HPLC data which are given merely to prove identification; (2) straight-line graphs; (3) generalized pH and temperature-denaturation curves of enzymes; (4) illustrations of IR, UV, NMR or MS (values can be quoted in the text or Experimental); (5) flow sheets illustrating isolation of compounds; (6) expectable MS fragmentation patterns; (7) formulae of well-known compounds or reaction schem~s; (8) tables giving either single values for each parameter which could be easily quoted in the text, or repeating data shown elsewhere.

Illustrations should be drawn on separate pages and prepared with good contrast (black on a white background). Lettering in tables, figures, etc: lettering in formulae, figure axes etc. must be large enough to be legible after reduction. Lettering should be drawn in 6-7pt Helvetica (Arial) font to ensure optimum visibility. Chemical formulae must be made absolutely clear; printers are not chemists and much delay is caused by poor drawing. Aromatic rings must be drawn with alternate double bonds and conformation of single bonds shown by thickened or dashed (III) lines according to convention. Formulae should be numbered consecutively in Arabic numerals. If graphics are created using ChemDraw or ISISDraw the preferred settings are: font 10 pt Helvetica (Arial), chain angle 120°

bond spacing 18% of length, fixed (bond) length 14.4 pt (0.508 cm), bold width (bond thickness) 2.0 pt (0.071 cm), line width 0.6 pt (0.021 cm), margin width 1.6 pt (0.056 cm), and hash spacing 2.5 pt (0.088 cm). The overall size should be not more than 95mm (single column) or 194mm (double column) by 285 mm.

Tables must be typed on separate pages, numbered consecutively, given a suitable caption and arranged to be viewed vertically. They must be so constructed as to be intelligible without reference to the text. Every table must have an Arabic number and a title, and each column must be provided with an explanatory heading. No vertical rules should be used. Tables should not duplicate results presented elsewhere in the manuscript (e.g. in graphs). Footnotes may be used to expand column headings, etc. and should be referenced by superscript lowercase letters a,b,c rather than symbols. Results should be cited only to the degree of accuracy justified on the basis of the errors of the method and usually only to three significant figures. Units must always be clearly indicated and chosen so as to avoid excessively high (>100) or low (<0.01) values. The figure zero should precede the decimal point for all numbers below one (e.g. 0.1).

Half-tone photographs must have good contrast and not be more than 25 cm wide and not more than 30 cm high. Original photographs (or high resolution graphic files of at least 500 dpi) must be supplied as they are to be reproduced (e.g. black and white or colour). If necessary, a scale should be marked on the photograph. Please note that photocopies of photographs are not acceptable.

Colour charges
Authors are encouraged to submit their works in colour. There is no charge for colour print.

Supplementary data
HKPJ now accepts electronic supplementary material to support and enhance your scientific research. Supplementary files offer the author additional possibilities to publish supporting applications, movies, animation sequences, high-resolution images, background datasets, sound clips and more. Supplementary files supplied will, subject to peer review, be published online alongside the electronic version of your article in HKPS website. The presence of these files will be signified by a footnote to the article title, and by a description included in a 'Supplementary Data' section at the end of the paper. In order to ensure that your submitted material is directly usable, please ensure that data is provided in one of our recommended file formats and supply a concise and descriptive caption for each file. Please also clearly indicate whether data files are either i) for publication online or ii) only to be used as an aid for the refereeing of the paper. For more detailed instructions please visit our Author Gateway at htto://authors.HKPJ.org

Errata and Corrigenda to publish articles will be included, at the discretion of the Section Editors and the publisher.

Abbreviations
About, approximately: ca.
Anhydrous: dry (not anhyd.)
Aqueous: aq.
Circular dichroism: CD
Concentrated (or mineral acids): conc.
Concentrations: ppm (or ppb), µM, mM, M, %, mol
Dry weight: dry wt; fresh weight: fr. wt
Electricity: V, mA, eV
Force due to gravity (centrifugation): g; rpm (revolutions min^{-1})
Gas chromatography: GC
Gas chromatography-mass spectrometry: GC-MS Trimethylsilyl derivative: TMSi (TMS cannot be used as this refers to the internal standard tetramethylsilane used in ^{1}H NMR)
High performance liquid chromatography: HPLC
Infrared spectrophotometry: IR
Length: nm, µm, mm, cm, m
Literature: lit.
Mass spectrometry: m/z $[M]^{+}$ (molecular ion, parent ion)
Melting points: uncorr. (uncorrected)
Molecular mass: Da (daltons), kDa
Molecular weight: M_r
Nuclear magnetic resonance: ^{1}H NMR, ^{13}C NMR, Hz, δ
Numbers: e.g. 1, 10, 100, 1000, 10000; per or $^{-1}$
Optical rotatory dispersion: ORD
Paper chromatography: PC
Precipitate: ppt.
Preparative thin-layer chromatography: prep. TLC
Radioactivity: dpm (disintegrations per min), Ci (Curie), sp. act (specific activity), Bq (1 becquerel = 1 nuclear transformation $sec^{-1)}$
Repetitive manipulations: once, twice, x3, x4, etc.
RR_t (relative retention time), R_1 (Kovat's retention index), ECL (equivalent chain length- term frequently used in fatty acid work)
Saturated: satd.
Solution: soln.
Solvent mixtures including chromatographic solvents: abbreviate as follows n-BuOH-HOAc-H_2O (4:1:5)
Statistics: LSD (least significant difference), s.d. (standard deviation), s.e. (standard error)
Temperature: (with centigrade), mp, mps, mmp, bp
Temperature: temp.
Thin-layer chromatography: TLC, R_f
Time: s, min, h, day, week, month, year
Ultraviolet spectrophotometry: UV, A (absorbance, not aD-optical density)
Volume: 1, (litre), µ1, ml
Weight: wt, pg, ng, µg, mg, g, kg

Inorganics, e.g. $AlCl_3$ (aluminum chloride), BF_3 (boron trifluoride), Cl., CO_3, H_2, HCl, $HClO_4$ (perchloric acid), HNO_3. H_2O, H_2O_2, H_2SO_4, H_3B0_3 (boric acid), He, $KHCO_3$ (potassium bicarbonate), $KMn0_4$ (potassium permanganate;), KOH, K-Pi buffer (potassium phosphate buffer), $LiAlH_4$ (lithium aluminium hydride), Mg^{2+}, $MgCl_2$, N_2, NH_3, $(NH_4)_2S0_4$, Na^{+}, $NaBH_4$ (sodium borohydride), NaCl, $NaI0_4$ (sodium periodate), NaOH, Na_2S0_3 (sodium sulphite), Na_2S0_4 (sodium sulphate), $Na_2S_20_3$ (sodium thiosulphate), 0_3, PPi (inorganic phosphate), SO_4^{2-}., Tris (buffer).

Organics, e.g. Ac_20 (acetic anhydride), n-BuOH (butanol), C_6H_6 (benzene), CCl_4 (carbon tetrachloride), CH_2Cl_2 (methylene chloride), $CHCl_3$ (chloroform), CH_2N_2 (diazo-methane), CM (carboxymethyl), DEAE (diethylaminoethyl), DMF (dimethylformamide), DMSO (dimethyl sulphoxide), EDTA (ethylene-diaminetetra-acetic acid), Et_20 (diethyl ether), EtOAc (ethyl acetate), EtOH (ethanol), $HC0_2H$ (formic acid), HOAc (acetic acid), iso-PrOH (iso-propanol), Me_2CO (acetone), MeCOEt (methyl ethyl ketone), MeOH (methanol), NaOAc (sodium acetate), NaOMe (sodium methoxide), petrol (not light-petroleum or petroleum ether), PhOH (phenol), PrOH (propanol), PVP (polyvinylpyrrolidone), TCA (trichloroacetic acid), TFA (trifluoroacetic acid), THF (tetrahydrofuran). ^{1}H NMR solvents and standards: $CDCl_3$ (deutero-chloroform), D_2O, DMSO-d_6 [deuterodimethylsulphoxide not $(CD_3)_2S0$], pyridine-d_5 (deuteropyridine), TMS (tetramethylsilane).

For further terms used in biochemistry and molecular biology the authors should see the websites of the nomenclature committees (www.chem.qmul.ac.uk/iubmb/).

Page charges.
There is no page charges for HKPJ.

Proofs and Articles in Press
Proofs will be despatched via e-mail to the corresponding author, by the Publisher and should be returned with corrections as quickly as possible, normally within 48 hours of receipt. Proofreading is solely the author's responsibility. Authors should ensure that corrections are returned in one communication and are complete, as subsequent corrections will not be possible. Any amendments will be incorporated and the final article will then be published online as an Article in Press.

Offprints
Two copies containing the offprints will be supplied free of charge. Additional offprints and copies of the issue can be ordered at a specially reduced rate using the order form sent to the corresponding author after the manuscript has been accepted. Late orders for reprints will incur a 50% surcharge.

Copyright
Upon acceptance of an article, Authors will be assumed to transfer copyright unconditionally to HKPJ. This transfer will ensure the widest possible dissemination of information. If excerpts from other copyrighted works are included, the Author(s) must obtain written permission from the copyright owners and credit the source(s) in the article.

Author enquiries
For enquiries relating to the submission of articles (including electronic submission) please send your query by email to editor@hkpj.org

A new treatment with added strength to help patients beat OAB* symptoms

TOVIAZ ABBREVIATED PRESCRIBING INFORMATION

1.TRADE NAME: Toviaz
2.PRESENTATION: Toviaz 4 mg tablets: light blue, oval, biconvex, film-coated, and engraved on one side with the letters 'FS'. Toviaz 8 mg tablets: blue, oval, biconvex, film-coated, and engraved on one side with the letters 'FT'.
3.INDICATIONS: Treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence) that may occur in patients with overactive bladder syndrome.
4.DOSAGE: Recommended starting dose is 4 mg once daily. Based upon individual response, the dose may be increased to 8 mg once daily. The maximum daily dose is 8 mg.
5.CONTRAINDICATIONS: Hypersensitivity to the active substance, peanut, soya or any of the excipients; urinary retention; gastric retention; uncontrolled narrow angle glaucoma; myasthenia gravis; severe hepatic impairment (Child-Pugh class C); concomitant use of potent CYP3A4 inhibitors in subjects with moderate to severe hepatic or renal impairment; severe ulcerative colitis; toxic megacolon.
6.WARNINGS & PRECAUTIONS: Clinically significant bladder outflow obstruction at risk of urinary retention; gastrointestinal obstructive disorders; gastro-oesophageal reflux and/or who are concurrently taking medicinal products that can cause or exacerbate oesophagitis; decreased gastrointestinal motility; autonomic neuropathy; controlled narrowangle glaucoma; hepatic impairment; renal impairment; concomitant administration of potent or moderate CYP3A4 inhibitors; concomitant administration of potent CYP3A4 inducers; concomitant administration of potent CYP2D6 inhibitors; patients with risk for QT prolongation and relevant pre-existing cardiac diseases; rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. Other causes of frequent urination should be assessed before treatment.
7.INTERACTIONS: Antimuscarinic agents and medicinal products with anticholinergic properties, medicinal products that stimulate the motility of the gastrointestinal tract, CYP3A4 inhibitors, CYP3A4 inducers, CYP2D6 inhibitors.
8.PREGNANCY AND LACTATION: Not recommended during pregnancy; breastfeeding is not recommended during treatment with Toviaz.
9.SIDE EFFECTS: Dry mouth, dizziness, headache, dry eye, dry throat, abdominal pain, diarrhoea, dyspepsia, constipation, nausea, dysuria, insomnia.

Reference: HK PI (version date Nov 2008)
Date of preparation: April 2011
Identifier number: TOV0411

FULL PRESCRIBING INFORMATION IS AVAILABLE UPON REQUEST.

TOV11002P

*OAB, overactive bladder

Pfizer

For more information, please contact:
Pfizer Corporation Hong Kong Limited
16th Floor, Stanhope House, 738 King's Road
North Point, Hong Kong
Tel: (852) 2811 9711 Fax: (852) 2579 0599

Toviaz®
fesoterodine fumarate
prolonged release tablets 4mg and 8mg

Powerful dose-dependent efficacy