HONG KONG PHARMACEUTICAL JOURNAL

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Pharmacists' Perception on Continuous Education

Menstrual Disorders

Systemic Antifungal (2 CE Units)

Management of Hypertension

Large-Scale Production of Erythropoietin

Therapeutic Effects of Ginger

Societies' Annual Reports

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References:
1. Vardenafil Summary of Product Characteristics, 2003
2. Stief C et al. Progres en Urologie 2003; 13(suppl 2):31 (abs 100)
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5. Brock G et al. The Journal of Urology 2003; 70:1278-1283

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Editorial

Continuing education is important to maintain the standard of a profession. Different pharmacy professional bodies, Pharmaceutical Society of Hong Kong (PSHK), the Practising Pharmacists Association of Hong Kong (PPA), the Society of Hospital Pharmacists of Hong Kong (SHP), the Chinese University of Hong Kong (CUHK) and the Hong Kong Pharmacists (Public Services) Association (HKP(PS)A) used to organize various continuing education (CE) activities for their own members. In year 2000, the Pharmacy Central Continuing-education Committee (PCCC) was established. Since then, the CE activities coordinated by this Committee became the mainstream education channel for more than 1,300 pharmacists in Hong Kong. The resources for preparing CE activities are also centralized and allocated efficiently. In the past three years, training on various topics was provided mainly in the forms of lectures and CE articles. In 2001, the HKPJ also became one of the channels to deliver training materials to our colleagues.

Prior to the launch of the PCCC program, a survey had been done to gauge pharmacists' opinion towards the unified program (HKPJ 2000;9:102-4). The survey results provided a solid foundation for the PCCC. It helped to align goals for the participating academic bodies. Besides, the CE activities can also be tailor made to the need and expectations of the local pharmacists. Entering the forth year of the unified program, it is about the right time to revisit how we have been doing. This issue's cover story reveals the perceptions of the Hong Kong pharmacists towards the continuing education program (page 6). In general, the PCCC program has been well received by the respondents. The results also verified the importance of continuing education in our professional life. In that article, you can also find some suggestions on the future modes of CE program, such as the provision of on-line based training and clinical workshops, and including postgraduate courses in the PCCC program.

In the future, what is the role of PCCC in the pharmacy professions? Will the participation be mandatory and become a part of the professional registration renewal? There are lots of controversies on how to implement the idea, not only in Hong Kong, but also in many other developed countries. With no doubt, personnel continuous training reflects standard and quality. So, let's learn from the quality control of other pharmaceutical-related professions... Cheung HY *et al* (HKPJ 2002;11:155) introduced computer-based training kits with self-assessments for fulfilling Good Manufacturing Practices (GMP) requirements. Lai and Cheung (HKPJ 2003;12:26-9) advocates laboratory accreditation for testing Traditional Chinese Medicines on the top to following the GMP requirements. Lau and Lee (HKPJ 2003;12:49-51) also encourages a voluntary accreditation scheme to improve pharmaceutical care in old age homes. "Legislation often set out minimal requirements to be achieved... punitive approach my not help in continuous quality improvement... Accreditation may then become a symbolic of quality guarantee," the authors expressed in the article.

Perhaps, as time goes on, and more discussion or consultation carried out among the pharmacists, it will be revealed how the continuing education is positioned in the registration renewal in order to enable us to face the challenge ahead.

Let's turn from training into daily practice. The end results of a good CE training should be good quality services and benefits brought to the community. During the past 12 months, we experienced a great deal of negative impacts from SARS and avian flu. However, these events awaken our sense of mission as a member of health care providers. From the annual reports of the three mother societies' (page 40-42), we can see that tremendous works have been done. Yet, both our professional value and image were synergized by the efforts from Drug Education Resource Centre (DERC) and individual pharmacists' in various direct-to-public health promotion activities. The list of educational programs coordinated by DERC is so long that we are not able fit into this issue of HKPJ. We would like to send, to DERC and SHP, our apologies (for not publishing the complete list) and our sincere congratulations (for all the great work done)!

Nowadays, primary care policy and service development increasingly focus to shift from public to private where improved access and choice can be provided. It cannot, however, happen overnight, but in a step-by-step approach. In fact, something has been going on with the launch of the Public Private Partnership Program (4P). In the previous issues of the HKPJ (Sep 2002 and Apr 2003), we have published some early activities under this program. You may want to revisit the development of the initiative, and keep up with the up-to-date progress in the article published this quarter (page 43). Pharmacists should take this opportunity to shout loudly on what they can contribute in the public health arena through active participation, no matter the contribution is small or its remit is board. The pharmacy profession will be respected in the future health care reform, only if we are shiny enough today.

Michael Leung
Managing Editor

The Perceptions of Pharmacy Continuing Education in Hong Kong

Tsang, YWW; Fok, SMM

I INTRODUCTION

The American Public Health Association (2004) proposed the objectives of providing journal-based education to physicians are to maintain, develop, or increase their knowledge, skills and professional performance in the domain of public health. Journal-based education is one of the options of providing continuing education to health care professionals in the medical discipline, in the pharmacy discipline and in others. In Hong Kong, the Pharmacy Central Continuing Education Committee (PCCC) is responsible for providing continuing education and for accrediting continuing education units (CEUs) to registered pharmacists. Modes of educational activity that can be accredited for CE units include seminars, workshops, educational conferences and journal articles. The units that can be obtained from different activities are varied from 2 to 10. Apparently the participation of local pharmacists in these educational activities is active and the quality of the activities is well received. However a systematic and formal feedback with respect to the perceptions of registered pharmacists in Hong Kong of the roles of the PCCC as well as the need of CE has not yet been obtained. It is timely, therefore, to study this aspect in order to measure the roles of the PCCC and assess the needs of the pharmacists regarding their continuing education, and, last but not least, to further improve the quality of the educational activities so as to help the pharmacists maintain their core competencies. The aim of this paper is to report the findings of the perceptions of the local pharmacists of the above aspect.

II OBJECTIVES OF THE STUDY

1. To investigate the perceptions of the pharmacists in Hong Kong towards CE
2. To explore the factors affecting the perceptions of the pharmacists towards CE
3. To identify the merits of CE in the pharmacy profession in Hong Kong
4. To identify the aspects that can improve the future quality of the CE in pharmacy in Hong Kong

III RESEARCH DESIGN AND METHOD

i) Research design

A survey design was employed in the study.

ii) Method

a) Sample
All members of the PCCC were invited to participate in the study. The number of the members is approximately 800 during the period this study is conducting. Letters for invitation to participate in the study attached with questionnaires were sent to the addresses of all members registered in the Committee.

b) Instrument
A validated instrument which was developed by the PCCC recently to investigate the perceptions of pharmacy continuing education was adapted in the present study. For the purposes of this study, minor modification was made that the demographic characteristics of the respondents were addressed. Face validity was achieved in the executive committee of the PCCC. The questionnaire is a 19-item questionnaire. The first five items refer to relevant demographic characteristics of the subjects. These are types of practice setting, length of registration, number of seminars participated in the preceding 3 years, number of articles returned to the PCCC in the preceding 3 years and the receipt of CE certificates. Item 6 to item 16 are attitudinal statements which explore the perceptions of the members towards the PCCC. Item 17 to item 19 are open-ended questions to investigate the merits of the PCCC and areas for further improvement.

c) Procedure
The questionnaires were sent by post to all members attached with invitation letter stating the purposes of the study. Members were asked to send their responses to the Committee by fax. It took about a month for the return of the questionnaire.

IV RESULTS

One hundred and nine members returned their responses to the Committee. Despite the rather low respondent rate, i.e. 14%, the sample represented more than 10% of the total population.

i) Demographic characteristics

The demographic characteristics of the respondents that were obtained in the present study included practice setting, length of registration, number of seminars participating in the preceding three years, number of articles returned to the PCCC and receipt of the CE certificates. These items were considered to be important as they might affect the perceptions of the pharmacists towards CE. The practice settings in which the respondents are currently working are presented in Table 1. It can be seen that community sectors and hospitals were the common sectors in which the respondents are currently working.

Table 1. Practice settings in which the respondents are currently working (N=109)

Practice setting / Frequency	Number of pharmacists	Percent	Cumulative percent
Academic institutions	1	0.9	0.9
Community sectors	40	36.7	37.6
Government sectors	4	3.7	41.3
Hospitals	48	44	85.3
Manufacturing companies	9	8.3	93.6
Others	7	6.4	100.0
Total	109	100.0	–

Approximately, 60% of the respondents have less than 10 years of practising experience in pharmacy (Table 2).

It can be seen that the frequency of seminars attended by the respondents varying from 1-5 times, 6-10 times and more than 10 times was evenly distributed (Table 3).

Nearly 35% of the respondents did not return articles to the PCCC but nearly 34% did return 1 to 5 articles to the PCCC. Twenty percent of the respondents returned more than 10 articles to the PCCC and the attitude of this group of pharmacists seemed to be very active (Table 4).

The PCCC issue CE certificates to those members who have successfully obtained 20 CEUs every year under normal circumstances. Therefore for those respondents who gave positive response to this item implied that they have completed 20 CEUs every year while those who did not complete were not issued the CE certificates. The responses are presented in Table 5. Interestingly, the number of respondents who have received the CE certificates was nearly the same as those who have not.

Table 2. Length of registration (N=109)

Length / year	Number of pharmacists	Percent	Cumulative percent
< 5 years	36	33.0	33.0
5-10 years	26	23.9	56.9
10-15 years	20	18.3	75.2
> 15 years	24	22.0	97.2
Not registered	3	2.8	100.0
Total	109	100	–

Table 3. Number of seminars participated in the preceding 3 years (N=109)

Number of seminars/ Frequency	Frequency	Percent	Cumulative percent
None	7	6.4	6.4
1-5	35	32.1	38.5
6-10	30	27.5	66.1
>10	37	33.9	100.0
Total	109	100.0	–

Table 4. Number of articles returned to the PCCC (N=109)

Number of articles / Frequency	Frequency	Percent	Cumulative percent
None	38	34.9	34.9
1-5	37	33.9	68.8
6-10	10	9.2	78.0
>10	24	22.0	100.0
Total	109	100.0	--

Table 5. Receipt of CE certificates (N=109)

Response / Frequency	Frequency	Percent	Cumulative percent
Yes	54	49.5	49.5
No	55	50.5	100.0
Total	109	100.0	

Table 6. Correlation between the demographic characteristics (DC) and the perceptions of the PCCC (N=109)

Correlation parameter	Practice setting	Length of registration	Seminar	Articles	Receipt of Certificate
coefficients	0.37	0.198	0.008	-0.080	0.94
p value	p=0.000	p=0.039	p=0.933	p=0.407	p=0.333

ii) Perceptions of the PCCC in Hong Kong

Item 6 to item 16 of the questionnaire were designed to investigate the impact perceived by the pharmacists of the PCCC on them. The themes of these items include personal and professional development, roles and functions of the PCCC. These items will be presented in the subsequent section. These 11 items are attitudinal statements which are in Likert-scale format ranging from "strongly disagree" to "strongly agree" with numerical values in ascending order from 1 to 5. The higher the score the more favourable the response is. The theoretical range of scores of these items is from 11 to 55. The highest score in this sample was 53 and the lowest was 33. The mean score was 42.56 (SD=4.25), the median was 43.0, the mode was 43 and the skewness was -0.64. It can be seen that the responses from the members to the PCCC are very positive.

iii) Correlation between demographic characteristics and perceptions of the PCCC

One of the objectives of this study was to explore factors affecting the perceptions of the pharmacists of the PCCC. The demographic characteristics of the sample were used as variables to study if a relationship exists between these variables and the pharmacists' perceptions of the PCCC. The Spearman Rank Correlation Coefficients were used to investigate the relationship. The results are presented in Table 6.

It can be seen that a very strong relationship (p = 0.000) was found between practice settings in which the members are currently working and their perceptions of the PCCC and so as a strong relationship was found between the length of registration and their perceptions. This implies that the types of practice settings and the practising experience of the pharmacists may affect their perceptions of the PCCC.

iv) Difference in perceptions of the PCCC between groups

Variables that may affect the pharmacists' perceptions of the PCCC were investigated in the above section. Among these variables, they were further divided into different types, such as the practice setting was divided into academic institutions, community sectors and hospitals, etc. Length of registration, seminar attendance and articles returned to the

PCCC were further divided into different length in years or numbers. In order to explore if a difference exists between the different types of practice settings, the different length of registration and the different number of seminar attendance and articles returned to the PCCC as well as receiving the CE certificates or not, Kruskal-Wallis test was applied to investigate this aspect. The findings are presented in Table 7. Between groups difference was only found in the different types of practice settings. This implies that respondents who are working in different practice settings present differences in their perceptions of the PCCC.

Although the 11 items were developed to measure the perceptions of the PCCC, no factor analysis was conducted to explore the factor structure of these items. In this study, Principal Component Analysis (PCA) was used to explore the factor structure of the 11 items.

Table 7. Difference in perceptions of the PCCC between groups of the same variable (N=109)

	Practice setting	Length of registration	Seminar	Articles	Receipt of Certificate
Chi-Square	21.315	4.488	0.328	0.858	0.946
df	5	4	3	3	1
p value	0.001	0.344	0.955	0.836	0.331

Table 8. Component weights of the 4 PCs

Item	PC1	PC2	PC3	PC4
6	–	–	–	0.869
7	0.715	–	–	–
8	0.751	–	–	–
9	0.608	–	–	–
10	–	–	0.646	–
11	–	–	0.554	–
12	0.600	–	–	–
13	–	0.645	–	–
14	–	0.600	–	–
15	–	0.603	–	–
16	0.710	–	–	–

Table 9. Variance explained by the 4 PCs

PC	Eigenvalue	Percent of variance	Cumulative percent
1	3.082	28.01	28.01
2	1.929	17.54	45.55
3	1.445	13.14	58.69
4	1.030	9.37	68.05

Table 10. The factor structure of the 4 PCs

PC1	**Personal and professional development**
Item 7	Continuing education can upgrade professional status
Item 8	Continuing education can improve our service to patients
Item 9	I agree with the way PCCC is providing CE opportunities through seminars and articles
Item 12	I have become more confident of my ability to pursue further learning
Item 16	I support continuing education for pharmacists
PC2	**Expectation of the PCCC**
Item 13	I have become more willing to consider different points of view in drug therapy
Item 14	PCCC should explore additional ways of providing CE
Item 15	PCCC should provide articles / seminars on the Internet
PC3	**Quality of programme**
Item 10	CE seminars held by the PCCC are appropriate in depth and variety
Item 11	CE articles provided by the PCCC are interesting and educational
PC4	**Responsibility of learning**
Item 6	I feel that I can take responsibility for my own learning

v) Factor structure of the attitudinal statements

As mentioned earlier, the responses of the respondents towards the 11 attitudinal statements were very positive. In order to investigate the themes represented by these 11 attitudinal statements, Principal Component Analysis (PCA) was used to explore the factor structure of the 11 statements. The analysis suggested 4 principal components (PC) which accounted for more than 68% of the total variation in the original variables. The component weights of the 4 PCs are presented in Table 8. The variance explained by the 4 PCs is presented in Table 9 and the structures of the 4 PCs are listed in Table 10.

With respect to the meaning of the items, four labels, namely "personal and professional development", "expectation of PCCC", "quality programme" and "responsibility of learning" were given to the 4 PCs. Although the factor structure was identified with the use of PCA and the results were satisfactory with respect to the total variation, the number of items to which the PCs belong, particularly the last PC seemed to be inadequate. This issue will be dealt in the discussion section.

vi) Continuing education programmes offered by the PCCC

In order to obtain more views of the respondents of the CE programmes offered by the PCCC, three open-ended questions were used in the last section of the questionnaire. These questions are presented as follows:

- What was the best aspect of continuing education programmes offered by the PCCC?
- Which aspect(s) is/are most in need of improvement?
- Any other suggestions/comments for the PCCC?

vii) The best aspect of continuing education programmes offered by the PCCC

There were 46 out of 109 responses to this question. A summary of the responses is presented in Table 11.

viii) Aspects that need improvement

There were 48 responses to the second question and 44 to the last question. Nearly all the respondents who were willing to respond to the second question were willing to respond to the last question. Most of the answers to the last two questions were overlapping. A summary of the descriptions of the answers is presented as follows:

The provision of:
- hard copies of the training materials
- contact persons
- additional quota for the programmes
- new drug information
- better quality of journals used in the programmes
- clinical workshops
- answer sheet for the journal-based programmes

Table 11. A summary of responses regarding the best aspect of CE programmes	
The best aspect	**Frequency**
The use of journal-based education	14
Regular organization of seminars	10
Continuation of up-dating professional knowledge	10
Promotion of partnership	4
Up-dating professional image	3
Maintenance of regular contact in the profession	2
Programmes are well organized and structured	1
Being kept informed of current affairs in the profession	1

- answers to the questions regarding the journal-based programmes
- on-line CE programmes
- mandatory CE programmes
- more lectures, seminars
- discussion forum
- postgraduate courses

In summary, the respondents demanded a variety of modes of CE programmes such as on-line programmes, clinical workshops, discussion forum and postgraduate courses in addition to lectures, journal-based education and seminars that are currently offered by the PCCC. They also demanded further information regarding the journals in terms of hard copies, better quality, answer sheet and answers to the questions. Two other significant aspects were the provision of contact persons and mandatory CE programmes.

IV DISCUSSION

The limitation of this study was the rather low response rate, i.e. about 14%. The possibility of the low response rate might be related to the loss of contact of the members. Although the number of members enrolled under the PCCC is about 800, apparently, the members who have actively participated in the CE programmes offered by the PCCC are about 300 to 400 with respect to the record of enrollment. Therefore not all of the members were active in participating in the CE programmes or some members might have changed their addresses without notifying the PCCC and might not receive the questionnaire. In future related research, more promotional activities are recommended in order to recruit more respondents.

Despite this limitation, the objectives of the study were achieved with the use of the instrument developed by the PCCC.

The respondents have shown a rather positive attitude towards the PCCC which is a good performance indicator. The merits of the PCCC and CE in the pharmacy profession perceived by the respondents included the personal and professional development, the provisions of quality programmes and the encouragement of responsibility of self learning. These aspects were identified with the use of PCA in analyzing the respective items. These findings supported the claim of Wilson and Wen (2000) that CE in pharmacy contributes career advancement, personal development and job satisfaction to the pharmacists. These findings also demonstrated that the questionnaire developed by the PCCC is a useful instrument to measure the perceptions of the pharmacists towards CE. However, further development of the instrument is needed particularly, more items should be added to the last two PCs in order to improve the usefulness of the instrument. Other related aspects were also identified in this study. It was found that the types of practice settings and the length of registration would affect the respondents' perceptions towards the PCCC and CE in pharmacy. Intriguingly, the respondents from different practice settings demonstrated differences in their perceptions of the related aspects. However the factors leading to their different perceptions cannot be investigated by the quantitative method, as it was used in this study. In order to explore further views of the pharmacists from different types of settings and have different length of registration towards the related aspects, it is recommended to conduct interviews with these pharmacists in the future.

In relation to the best aspect of the PCCC, the qualitative findings further supported the results of the previous items regarding the merits of the PCCC in relation to the quality of the programmes. The responses to the areas of improvement for the PCCC include innovative educational strategies such as on-line mode, clinical workshops and discussion forum. All the responses were value-added to the improvement of the roles and functions of the PCCC and the quality of the CE programmes offered.

In fact, a website for the PCCC is under construction at the moment and it aims to provide CE activities to all members of the PCCC in the near future. A clinical workshop is also planned to be held on the 24th of April 2004. The workshop aims to provide health assessment skills to our members and to familiarize themselves with the practical skills in handling equipment for asthma, hypertension and diabetes mellitus so as to enable our pharmacists who may participate in the "Public Private Partnership Program" run by the Hospital Authority.

VI CONCLUDING REMARKS

This preliminary study provides a picture of the pharmacists in Hong Kong towards their needs of CE in the profession. The findings were encouraging to the PCCC as their roles and functions in the profession are evident. Undoubtedly it provides further direction to the PCCC not only for future improvement but also for future development of the profession such as providing mandatory CE education in pharmacy.

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藥師 . . . 藥事 - *沉默的聲音*

凌浩明

親愛的藥劑師 ：

最近閱讀到一篇文章，覺得甚有意思。願與大家分享。

> 教授從兜裡掏出一張一美元的鈔票，高高舉起，漲紅了一臉，大聲說：「誰能提出一個問題，任何問題，我就獎給他一美元。」
>
> 他是美國人，在北京外國語大學任教。他講的是歷史與宗教，他講完了，問大家有什麼問題。誰也不吱聲。他請求大家提問，因為不然的話他無法了解我們聽懂了多少。但還是沒人舉手。教授有點不耐煩了。不，應該說，他憤怒了。他認為這是中國學生對他的不尊重。
>
> 「沒有哪一種知識是提不出問題的難道我講的每一句話都無懈可擊嗎？是你們壓根兒沒聽課還是愚不可及？」他的另一隻拳頭敲打桌面。
>
> 課堂的空氣很緊張，學生們被嚇壞了。我們從幼兒園開始就被訓練雙手背後，認真聽講，長大後開始記筆記。誰記得全、背得好，考試就能拿高分。提問的通常是老師。他期待學生們還給他曾授予學生的正確答案。是的，中國的學生，起碼我們這一撥人，在十幾年嚴格的教育中學會了如何對付老師的提問，更不被許可反問，那樣是有悖師生之道的。所以，在美國教授晃動的一美元下，我們有點兒不知所措。
>
> 終於有幾個學生舉手了。我是其中之一。與其說我們真的有計麼問題要問，不如說是因為我們也有點兒生氣，因為那一美元有點侮辱人。我們提出了問題，問了些什麼似乎並不重要，要緊的是提問本身。沒有人要那一美元。下課的時候，教授的臉色好看了一些，而我們也糊裡糊塗地昂頭，盤點靠提問贏得的一點兒民族自尊心。
>
> 那是十年前的事了。我上大學二年級的時候。
>
> 現在我已非常習慣於提問了。實際上。我已經以提問為生了。我是記者。

〔節錄自「楊瀾訪談錄」之自序〕

楊瀾女士是一位世界知名的新聞工作者。她曾經採訪過不少中國及海外的名人與政客。真想知道她描述的這事件有否影響了她日後職業的選擇。該美國教授也許幫了她一把，將她從「沉默」的壞習慣中喚醒了。

其實當我給本地藥劑學生講學時也經常出現同樣的難題。他們不會發問，亦不願回答問題，不管知道答案與否，當你提出一個問題時，他們有些會左顧右盼，其他則不安地坐著，眼睛集中於筆記上，並許願自己是透明的，不會被講師點中。

像那位美國教授一樣，我總對原因大惑不解。究竟同學們已瞭解課程的全部，還是他們甚麼也不明白？是他們不想浪費大家時間，是他們覺得答案太簡單而不屑回答，還是怕答錯以致當眾出醜？他們會與鄰座同學竊竊私語，或寧願待課後與講師接觸，卻不願在課堂內與大家分享問題，互相學習，一同研究。那是何原故呢？無論如何，這實非一群學識豐富，年青有為的專業人士應有的態度，也非藥劑行業之福。

我相信此現象與中國人數千年的封建文化有關。一直以來，做臣子的都不敢抗拒君主之命，為兒女者也不可忤逆父母之言，對師長要遵循教誨，見前輩須唯命是從，發問或建議幾乎是大逆不道之事。

此外，香港中、小學的填鴨式教育制度也助長了這種陋習。老師備課不足，或課程緊迫，都會使為師者不鼓勵提問。

如果我們的年輕畢業生將會在實驗室裡工作，整天與試管或豚鼠為伍，那還可以。可是，大多數藥劑畢業生都嚷著要當臨床藥劑師，或跑到診所和社區藥房服務病人。無論他們以藥品推銷為業，或是被晉升為經理而要與醫生、護士和其它行政人員開會，如果他們不學會了在恰當的時機提出問題，並對別人的提問予以迅速及果斷的回應，又怎可當此重任？別人又怎會尊重他們呢？

其實正在執業的藥劑師們也好不了多少。在會議室中，在研討會上，敢發言或提問的寥寥可數，往往都是那兩三位「問題人物」、「好知之徒」。

雖然沉默的種子早已種植在我們的腦子裏，我們甚至不能原滿解釋為何這樣。但無論如何，這種「學而不問」，「會而不議」的態度，正損害著我們專業化的進程。

我們故然要學會得體地表達和站起來說話的勇氣。而為師者也應鼓勵學生提問和發表意見，在會議桌上前輩們亦應細心聆聽新進們的聲音，多提點，少批評，讓老、中、青都敢百花齊放，共商大計。

最後，那位美國教授也惱得有理：對別人的提問毫無反應基本上是一種不尊重的行為。這是三歲孩童也曉得的禮貌！

凌浩明

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Menstrual Disorders

Chan, Windy

The menstrual cycle is a rapidly changing biologic process involving extensive systems and chemicals in the body. This article describes several periodic menstruation-related problems experienced by women and their treatments.

Extracted from http://www1.renminbao.com/rmb/articles/2002/11/27/24057pb.html

I DYSMENORRHEA

Dysmenorrhea refers to menstrual cramps occurring just before and/ or at the onset of menses

Prevalence of dysmenorrhea grows from early to late adolescence and declines after age 30 to 35. In younger women, there is often no known pathology associated with the pain (primary dysmenorrhea). Overproductions of prostaglandin ($PGF_{2\alpha}$\ and PGE_2), leukotrienes, and vasopressin have been proposed for the pain and uterine contractions. [1] Mild to moderate cases can usually be managed by over-the-counter (OTC) medicines. Sometimes, more commonly seen in older women age 30 to 45, dysmenorrhea is due to underlying anatomic and/ or pelvic pathology, such as uterine fibroids, endometriosis, and pelvic inflammatory disease (secondary dysmenorrhea).[2] Medical referral is required for diagnosis. (Table 1)

Other symptoms of primary dysmenorrhea include backache, headache, faintness and gastrointestinal (GI) disorders like bloating, nausea, vomiting and diarrhea. Treatment aims to alleviate symptoms for maintaining daily functioning.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs inhibit prostaglandin synthesis and exhibit anti-inflammatory, analgesic, and antipyretic activity. They are rational choices for controlling the painful cramps.[3] Diclofenac, ibuprofen, ketoprofen, meclofenamate, mefenamic acid and naproxen are the NSAIDs specifically approved by the US Food and Drug Administration (FDA) for treatment of dysmenorrhea. They have been reported to be effective in reducing menstrual pain, as well as breast tenderness, bloating, irritability, and depression. [4] For prompt rescue from moderate dysmenorrhea, NSAIDs should be started three to seven days prior to expected menses and continue until flow stops.

Since the NSAIDs are usually used for short periods in otherwise healthy young women, they are generally well tolerated and free of serious toxicity. GI upset is the most common adverse effect associated. NSAIDs are to be avoided in patients with history of allergy, underlying GI diseases and asthma. In community setting, ibuprofen, possessing the most favorable risk-benefit ratio, is the drug of choice. As individual patient response varies, trials of several agents may be required for finding the helpful ones.

For those who cannot tolerate NSAIDs due to GI adverse effects, the cyclooxygenase-2-specific (COX-2) inhibitors can be alternative agents. Paracetamol has little effect on the prostaglandins and so it is theoretically less reliable than NSAIDs. However, it is a useful substitute when NSAIDs are contraindicated.[4] (Table 2)

Oral contraceptives (OCs)

OCs have different mechanisms of action from NSAIDs and can be used adjunctively in refractory cases. They inhibit ovulation and thereby elude prostaglandin production in the late luteal phase. This generally significantly reduces the amount of

Table 1. General differentiation of symptoms

	Primary dysmenorrhea	Secondary dysmenorrhea
Nature of pain	◆ Spasmodic, cramping pain in lower abdominal and suprapubic area, which may radiate to the back or thighs	◆ Dull, aching pain which can occurs in lower abdomen and lower back
	◆ Pain begins during the day before bleeding starts; eases gradually and often diminishes in one to two days	◆ May occur during other parts of the menstrual cycle and may be relieved or worsened by menstruation
Patient	◆ Younger women	◆ Older women, especially in those who have had children
Others	–	◆ Vaginal discharge in addition to pain (in pelvic infection)

Table 2. Analgesics and dosing regimens for primary dysmenorrhea [3,4]

Analgesics	Dosing regimens
NSAID	
Diclofenac	50mg TID (max: 150mg/day)
Ibuprofen	200-400mg Q4-6H; or 600mg BID (max: 1.2g/day)
Mefenamic acid	250-500mg TID (max: 1g/day)
Naproxen	500mg, then 250-500mg BID (max: 1250mg/day)
Naproxen Sodium	500mg, then 275-550mg BID (max: 1375mg/day)
Cox-2 selective inhibitor	
Rofecoxib	50mg Daily
Celecoxib	200mg BID
Other	
Paracetamol	500mg Q4-6H (max: 4g/day)

menstrual flow, alleviating the painful cramps in primary dysmenorrhea.[1] OCs may be an appropriate treatment choice for dysmenorrhea in patients who do not wish to conceive though FDA approval is not granted for this indication. During the first few cycles initiating OCs, combination use of NSAIDs may be necessary for adequate relief.

On the contrary, if a woman, who has been taking OCs, presents with the symptoms of dysmenorrhoea, should probably best be referred to further medical investigation since the symptoms of primary dysmenorrhoea should have been reduced or eliminated by the use of OCs.

II MENORRHAGIA

Menorrhagia refers to abnormal menstrual bleeding (excessive bleeding or prolonged menses, periods too close together, and bleeding between periods).

Disturbed hormone levels usually accounts for irregular cycles and the induced menorrhagia. When it is due to local uterine mechanisms or prostaglandin effects, it is called dysfunctional uterine bleeding (DUB). Other causes of abnormal bleeding include uterine fibroids, endometriosis, endometrial polyps, and use of intrauterine device.

For ovulatory menorrhagia (heavy menstrual bleeding), treatment approaches include NSAIDs, hormone-based therapies such as OCs and antifibrinolytic drugs e.g., tranexamic acid. NSAIDs will decrease menstrual bleeding. For moderate cases, maximal doses should be taken on the beginning one to two days prior to menses.

III AMENORRHEA

Amenorrhea means absence of menstruation.

For young women who haven't started menstruating by age 16, medical referral is necessary to identify the underlying problem. In women who used to have a regular period, causes of amenorrhea include pregnancy, breastfeeding, extreme/ sudden weight loss, eating disorders, excessive exercising, or stress. Hormonal problems (involving the pituitary, thyroid, ovary, or adrenal glands) or problems with the reproductive organs may also be involved.

IV PREMENSTRUAL SYNDROME

Premenstrual syndrome (PMS) is the cyclic recurrence during the luteal phase (second half) of a combination of menstruation-related psychological, behavioral, and physical symptoms. Symptoms are most common in the week or two weeks prior to menses and fades out at or within several days of bleeding. PMS can affect menstruating women of any age until revolving with menopause.

The more severe and disabling end of PMS, premenstrual dysphoric disorder (PMDD), is associated with significant mood and anxiety symptoms and marked impairment in social or occupational functioning (Box 1). PMS/ PMDD is diagnosed based on daily symptom ratings obtained over the course of several menstrual cycles and the absence of concurrent disorders that are premenstrually exacerbated.

Box 1. What is Premenstrual Dysphoric Disorder (PMDD)?

PMDD is a severe, disabling form of PMS. Symptoms include both mood disorders (depression, anxiety, tension, and persistent anger or irritability) and physical symptoms (headache, joint and muscle pain, lack of energy, bloating and breast tenderness). Criteria of PMDD are listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). A woman must have at least five of the typical symptoms occurring during the luteal phase.

Symptoms

PMS often includes both physical and emotional symptoms. Majority of women experience negative changes in mood, appetite, sleep, and energy. More than a hundred of nonspecific symptoms have been reported and some of the more common ones are presented in Table 3.

If PMS is considered to be a possibility, pharmacist should advise the woman to keep a diary of symptoms, recording the natures, frequencies and durations, which are useful for further medical diagnosis and management. Women expressing cyclic mood symptoms may have PMS, other mood disorders, or both. Adequate assessment and differentiation must be performed for accurate diagnosis before selection of appropriate therapies.

Etiology and treatment

There is yet no universally accepted etiology for the syndrome. Theories put forward include imbalance in estrogen-progesterone activity, deficiency in essential fatty acids, and excessive secretions of neuropeptides and prostaglandins. Stress does not seem to cause PMS, but may make it worse.

Given that there are various proposed theories, it is not surprising that numerous measures have been put forward for PMS. However, none of these is consistently effective. For mild to moderate PMS, supportive, lifestyle, and dietary interventions should be the primary preference. For severe PMS/ PMDD, SSRIs are the initial drug of choice.

i) Nonpharmacological approach

Nonpharmacological approach is the first line intervention for PMS. Although there is no definitive supporting evidence

Table 3. Common symptoms of premenstrual syndrome (PMS)

Common symptoms of PMS include:
△ Fluid retention
△ Breast tenderness
△ Fatigue, generally low in energy
△ Insomnia; sleep disturbance
△ GI disturbance (bloating, constipation or diarrhea)
△ Various types of pain syndromes e.g., headache, joint or muscle pain
△ Appetite changes, food cravings
△ Tension, irritability, mood changes; anxiety or depression

from large trials, sufficient mechanistic evidence and epidemiological results support their effectiveness. Educate the patients about the disorder and encourage dietary modification and exercise. Assurance and support is important for coping with the disorder.

The following are a few commonly adopted lifestyle modifications recommended. [5, 6]

1. Adequate rest and sleep; good stress management
2. Regular conditioning or aerobic exercise with an increase in the premenstrual week (help raising endorphin levels which improve mood)
3. Well-balanced, scheduled meals with adequate fiber, protein, carbohydrates, vitamins, calcium, and minerals
4. Reduced intake of salt, caffeine, fat, and simple sugars (reduce severity of water retention)
5. Reduction of alcohol, caffeine, nicotine and drugs of abuse

ii) Pharmacological approach

Pharmacological approach should be initiated when symptoms are not sufficiently managed by the lifestyle modifications. The chronic nature of this syndrome makes both cost and side effects become the two important considerations of treatment choices.

a) Vitamins and minerals
Vitamin B_6 (pyridoxine) has been recommended for women taking oral contraceptives and estrogen therapy because estrogenic substances increase the demand for pyridoxine. There is some evidence that pyridoxine may be of benefit in treating premenstrual symptoms and depression though conclusion is limited by the controversies of trials. No confirmation of significant benefit is concluded in a review of studies conducted in the 1980s [7]. Whereas in a more recent review, the pooled results of nine studies (though generally of low-quality) supports benefits of pyridoxine supplements. [8] Women should be advised to observe the recommended dose; higher doses are reported to have led to peripheral neuropathy.

A few minerals such as calcium and magnesium have been reported to lessen premenstrual mood changes, fluid retention, and pain. In a well-designed trial, calcium therapy (1200mg/ day) showed more than 50% improvement in the PMS symptom complex scores (including negative affect, fluid retention and menstrual pain) in more than half subjects. [9]

In addition to their possible specific benefits in reducing premenstrual symptoms, dietary supplements generally help in women having poor appetite and low energy, especially in suffering PMS. (Table 4)

b) Evening Primrose Oil
Many women seek natural/ herbal alternatives for PMS and evening primrose oil (EPO) has been marketed for this syndrome.

In a few studies, EPO has been reported to improve PMS symptoms such as breast tenderness, mood change and bloating. However, results of most studies have been inconclusive and its application remains a subject of debate. It may work by increasing the level of prostaglandin E, which appears to be depleted in some women with PMS. The active component of EPO is gammalionlenic acid which is believed to reduce the response to hormones and prolactin. A review concluded that it is most likely not beneficial, or at best possesses only marginal benefit. [5] EPO, generally recommended in a dose of 500mg three times daily, has no apparent toxicity but is somewhat expensive. It may take several cycles to have noticeable improvements. Schizophrenic patients and those receiving epileptogenic drugs should avoid EPO which may manifest temporal lobe epilepsy.

c) NSAIDs, OCs and anti-depressants
NSAIDs and OCs are employed on the same ground as for dysmenorrhea. NSAIDs, being prostaglandin inhibitors, have been shown to reduce the intensity of both the physical and emotional symptoms as compared with placebo. [5, 10] They are to be begun approximately seven to ten days prior to and continued through the first few days of menses so as to have an impact on dysmenorrhea as well (For dosage, please refer to Table 2).

OCs continue to be widely prescribed for PMS though lacking extensive convincing evidence from studies. OCs may provide relief by suppressing ovulation but efficacies among formulations are also not yet defined. Women experiencing cyclic physical symptoms, such as dysmenorrhea or breast tenderness, may benefit most from OCs therapy, whereas those with mood symptoms of PMS may not improve and may even be at risk of side effects on emotions. [11]

For moderate to severe PMS/ PMDD, psychotropic agents are needed for the associated mood change and depression. *Selective serotonin reuptake inhibitors* (SSRIs) are the antidepressants of choice and seem to be more effective than buproprion or noradrenergic antidepressants. Their efficacy for physical and behavioral symptoms is still being defined but these agents are certainly effective for the mood symptoms. [12] The FDA has approved two such agents for treatment of PMDD - *sertraline* (Zoloft) and *fluoxetine* (Sarafem).

V PERIMENOPAUSE AND MENOPAUSE

Perimenopause (or premenopause) is the transition preceding to menopause which generally occurs between age 47 and 53. By definition, menopause is diagnosed after six months of amenorrhea.

During this transition, the ovarian function undertakes an erratic change. The number of functioning ovarian follicles gradually diminishes during a women's reproductive life, and in perimenopause, the decline becomes more rapid; by menopause, only a few follicles remain.

The switch is associated with irregular menstrual cycles, worsening of premenstrual symptoms and vasomotor complaints. Symptoms can be disturbing and difficult and progress as the estrogen and progesterone levels decrease. (Table 5; Box 2)

Before 2002, initiating hormonal replacement therapy (HRT) had been a well-accepted option to cope with menopause. Until, the findings in the Women's Health Initiative Study awoke millions of women. Some women decide not to take HRT and turn to the so-called natural products for help. Subsequently, numerous OTC herbal products have been heavily advertised to ease menopausal symptoms. Popular herbs used for menopausal problems include black cohosh, chast tree berry, dong quai, EPO, ginseng, licorice, red clover, and soy. Clinical studies on the effectiveness of back cohosh and soy appear to be mostly positive, whereas the studies on others have been mostly negative.

Soy (isoflavones/ phytoestrogens)

High dietary intake of soy products in Asian women has been proposed as one reason for the lower prevalence of hot flushes than of the Western counterparts. Soy contains isoflavones, in particular genistein and daidzein,

Table 4. Vitamins and minerals for premenstrual syndrome

Medications	Dosage
Pyridoxine	50-100mg/day (>200mg/day associated with risk of peripheral neuropathy)
Calcium (Elemental)	1.2-2.5g/day in divided doses for PMS
Magnesium	50-100mg BID; up to 360mg/day in divided doses during luteal phase of PMS

which have been investigated for their estrogen-modulating effects in the treatment of menopausal symptoms. Isoflavones are polyphenol compounds structurally related to estrogens that have been shown to bind to estrogen receptors, acting as partial agonists in some tissues and antagonists in others.

There was a substantial body of evidence, mainly from epidemiological studies, suggesting that isoflavones offer benefits. Nevertheless, some published data from trials showed only modest and short-acting (about six weeks) improvement in the severity of hot flushes, which, interestingly, also occurred in most of the placebo groups. [13] Results from one recent trial found that isoflavone supplements made from red clover did not help in menopausal symptoms. [14] Additional studies are warranted to differentiate active components among whole foods, soy protein, and isoflavone extracts.

In view of its safety profile and low cost, as well as the potential benefits in bone density and lipid profile, soy remains a favorable option to managing hot flushes and menopausal symptoms. Specific recommendations have yet to be made for optimal dosage regimen. The reasonable consumption is between 40 and 60 gram daily or isoflavones 200mg daily. It should be emphasized that while supplementing daily diet with beans or bean products is a benign intervention, no such presumption of safety can be made for the isolated isoflavone OTC products. Doses large enough to have symptomatic relief are likely to also produce estrogen-related side effects such as endometrial stimulation.

Black cohosh

Black cohosh, traditionally used by the Native Americans, is one of the most studied and perhaps most popular herbs for gynecologic problems in US. [13] Neither the identification of active compounds nor the mechanism of action is defined. A standardized product, Remifemin, is available in the market and has been used in most of the concerned studies.

Several studies, including a total of more than two thousand of menopausal women, have been conducted for comparing black cohosh with placebo, estrogen replacement therapy and diazepam. Black cohosh was found to be beneficial for treating hot flushes and night sweats. But most have an open or uncontrolled design or both, making assessment of efficacy potentially biased. [13]

In those studies, black cohosh exhibits good safety and tolerability profiles provided that no clinical trials have lasted for more than six months. There are no published data from human trials about long-term safety, particularly regarding endometrial or breast stimulation while effects on vaginal epithelium are inconclusive. Some documented adverse effects include bradycardia, dizziness and GI upset. When prepared in tablet, the usual dosage is one to two mg of 27-deoxyacteine daily. (For Remifemin, the usual dosage is 40mg twice daily)

Table 5. Influences of menopause

Influences	Descriptions
Vasomotor symptoms	Hot flushes; night sweats
Atrophic symptoms:	Vaginal dryness, pruritus, irritation, and dyspareunia; urinary frequency, dysuria, incontinence; decreased libido and increased incidence of cystitis
Emotional and cognitive symptoms	Lability, irritability, depression, poor concentration, anxiety attacks and sleep disturbance
Increased risk of coronary artery disease	--
Osteoporosis	50% of postmenopausal bone loss occurs in the first 7 years

Box 2. Tips for menopausal symptoms

Hot Flashes

- *Avoid triggering factors (hot environment, hot or spicy foods, alcohol, or caffeine; and stress)*
- *Maintain good ventilation at home and in workplace*
- *Avoid heavy clothing*
- *Regular exercise and relaxation*

Difficulty Sleeping

- *Daily physical activity of at least 30 minutes but avoid vigorous exercise too close to bedtime*
- *Avoid alcohol, caffeine, large meals, and working right before bedtime*
- *Drink something warm before sleeping such as herb tea or warm milk*
- *Keep bedroom at a comfortable temperature and a place solely for rest*
- *Avoid napping during the day*

Dong quai

Dong quai is a Chinese herb mostly used as part of a mixture as tonic for women. It is not considered estrogenic and is not usually prescribed alone in Traditional Chinese Medicine.

One trial, comparing isolated dong quai root with placebo, found no benefit for hot flushes though the 4.5-gram dose used was lower than that typically given in Chinese medicine. [13] Dong quai contains coumarins and thereby should avoid concurrent administration with anticoagulant therapy. It is contraindicated in hemorrhagic diseases and during colds or flu. Other more specific adverse effects are photosensitization and possible fever effect. [15]

VI FOR PHARMACISTS...

Pharmacists should be aware that while women using those 'natural' products may take it for years; most trials lasted only a few months. They should not be presumed to be safe until appropriate safety studies are carried out. Additionally, questions remain in the optimal dosing regimen. It is suggested to follow the manufacturers' instructions provided that reliable brands are identified.

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Wound Dressings

Poon, Tammi

I INTRODUCTION

A wound can be defined as a defect or break in the skin that results from physical, mechanical or thermal damage, or that develops as a result of the presence of an underlying medical or physiological disorder. The objective of any wound management regimen is to heal the wound in the shortest time possible and with minimum pain, discomfort and scarring to the patient.

In the community setting, pharmacist is the key person in assisting patients with questions regarding wound care procedures. It is important for us to familiarize with the existing range of wound management products, which can facilitate our choice in initiating and maintaining the optimal microenvironment for wound healing.

II IDEAL WOUND DRESSINGS

Effective wound management relies heavily upon the selection and application of an appropriate wound dressing. An ideal dressing should provide an environment at the surface of the wound in which healing may take place at the maximum rate consistent with the production of a healed wound with an acceptable cosmetic appearance. The characteristics of an ideal dressing are:

- Maintains moist environment at the wound dressing interface
- Provides thermal insulation
- Low or non-adherent
- Requires infrequent changing
- Provides mechanical protection
- Free from particulate contaminants
- Safe to use (non-toxic, non-sensitizing, non-allergenic)
- Comfortable and mouldable
- Good absorption characteristics (for exuding wounds)
- Impermeable to micro-organisms
- Acceptable to the patients, e.g. provide pain relief
- Cost effective
- Sterile
- Available in a suitable range of forms/sizes

III PRIMARY WOUND CONTACT MATERIALS

Dressings that are used to absorb exudates are often highly absorbent, but exhibit a tendency to adhere to the surface of the wound as fluid production diminishes. The use of a suitable wound contact material interface can help to overcome this problem. This layer must be sufficiently porous to allow the passage of blood or exudates away from the surface of the wound into the secondary dressing, in order to prevent maceration of the underlying tissue.

Primary wound dressings can then be further categorized as either passive or interactive. A passive dressing is one that simply protects the wound surface by covering it and protecting against dehydration. Interactive dressings are those that are able to actively interact with wound surface in order to promote an environment that maximizes healing potential.

There is a wide variety of dressing products currently available in the market. To simplify the selection of wound management products, dressing are being grouped according to generic name. The general properties, clinical indications and examples of products available in each generic group of dressing will be discussed in the following one by one.

i) Tulle (non-medicated) dressings

Tulle dressings are open mesh, cotton, rayon, viscose or gauze impregnated with white or yellow soft paraffin (tulle gras literally means "greased net"). These dressings are not highly absorbent and allow strike-through. Although paraffin reduces the adherence of the dressing, it should be removed with care, as it is not uncommon for patients to experience considerable pain when they are removed.

Tulle dressing is suitable for low to medium exuding wounds --- clean, superficial wounds, split thickness skin grafts and minor burns. Frequent dressing changes are required to avoid drying out and damage to granulation tissue.

Examples: Jelonet (Smith & Nephew)

ii) Tulle (medicated) dressings

These are tulle dressings with the paraffin base combined with a variety of antimicrobial agents e.g. chlorhexidine acetate 0.5%, framycetin or fusidin.

They are used clinically for the prophylaxis of topical treatment of wound infections. They can also be used for low to medium contaminated exuding wounds e.g. superficial traumatic wounds. Systemic absorption may occur in wounds covering 30% or more of the body surface. Problems of skin sensitivity and bacterial resistance may also occur with the use of antibiotics.

Examples: Bacitigras (Smith & Nephew)
Sofra-Tulle (Aventis)

iii) Low-adherent contact dressings

Low-adherent dressing pads are made from a variety of materials including cotton/acrylic fibres and knitted viscose. They are coated with either low-adherent materials or perforated plastic film and some may also have a simple fibrous absorbent layer.

Low-adherent dressings are intended for use on medium to exuding wounds e.g. surgical wounds healing by primary intention, superficial wounds. They can also be used to protect surgical incisions and recently healed wounds. Strike-through will occur when used to cover exuding wounds, necessitating dressing change. Securing with a secondary dressing, tape or bandages may also required.

Examples: Melolin (Smith & Nephew)
Telfa (Kendall)

iv) Vapour-Permeable films

Vapour- or semi- permeable films are transparent, thin, sterile films coated with hypoallergenic adhesive. They allow the passage of vapour but are impermeable to water and microorganisms. They are the most flexible of the products and can mould around elbows, heels and sacral areas.

They are suitable for wounds producing low amounts of exudates, e.g. superficial pressure sores, leg ulcers, surgical wounds, scalds, abrasions or minor lacerations. They can be used prophylactically to prevent pressure sores by reducing friction forces acting on the skin. They can also be used as a secondary dressing e.g. to hold hydrogel in place.

Examples: Tegaderm (3M)
Opsite Flexgrid (Smith & Nephew)

v) Foam Dressings

Foams consist of polyurethane foam or polyurethane foam film. They are dressings with a hydrophilic action providing a low-adherent wound contact layer. Some of these dressings have moisture-vapour-permeable backings which are hydrophobic and prevent vertical strike-through.

Foam dressings are suitable for use on light to medium exuding wounds e.g. pressure sores, leg ulcers, and burns. Most of them can be left in place for about 7 days, depending on exudates volume. Anatomically shaped dressings are available for sacrum and heel. The ease to release form fragile skin also makes them useful for patients with delicate or sensitive skin.

Examples: Allevyn range (Smith & Nephew)
Lyofoam (Seton)

vi) Alginate dressings

Alginate dressings are derived from seaweed. They produce a moist gel in the presence of exudates. Alginates rich in mannuronic acids (Algisite M) form soft gel; alginates rich in glucuronic acids (Kaltostat) form firmer gels.

Alginate dressing is capable of absorbing moderate to high levels of exudates. Once in place, the alginate fibres absorb exudates and tissue fluid to form a hydrophilic gel (through an ion exchange mechanism), which conforms to the wound surface. Once gel has formed, it facilitates autolytic debridement of moist slough and necrotic tissue.

Alginate is suitable for moderate to heavily exuding wounds e.g. pressure sores, leg ulcers and donor sites. If the dressing is applied to wounds with little or no exudates, burning sensation may by reported by patients.

Examples: Algisite M (Smith & Nephew)
Kaltostate (Convatec)

vii) Hydrogels

Hydrogels consist of insoluble polymers with hydrophilic sites, which interact with aqueous solutions, absorbing and retaining significant volumes of water.

There are two types of gel dressings. One has a fixed three-dimensional (3-D) macro structure and presented in the form of a thin flexible sheet. Hydrogels with a fixed 3-D macro structure do not change their physical form as they absorb fluid, although they may swell and increase in volume. The swelling process will continue until the gel becomes fully saturated or until equilibrium is reached. The other is amorphous hydrogel, which do not have a fixed three-dimensional macro structure. When these materials absorb fluid, they progressively decrease in viscosity and may flow to take up the shape of the wound that contains them. Amorphous hydrogels will continue to absorb fluid until the gels loses all its cohesive properties and simply becomes a dispersion of the polymer in water.

Hydrogel dressings provide many characteristics of the optimum environment for healing. Its fluid-donating properties facilitate autolytic debridement of dry and moist slough and necrotic tissue. It also rehydrates dry wounds and promotes pain relief by keeping exposed nerve ending moist.

Sheet hydrogels can be used in low to moderately exuding flat wounds e.g. pressure sores, leg ulcers, minor burns and traumatic wounds. Amorphous hydrogels can be used in low to moderately exuding wounds, necrotic or sloughy wounds e.g. pressure sores, sinuses, cavity wounds, extravasations injuries.

Examples: Intrasite gel (Smith & Nephew)
Nu-gel (Johnson & Johnson)

viii) Hydrocolloid

Hydrocolloid is a family of wound management products manufactured from gel forming agents such as carboxymethylcellulose, pectin and gelatin in an adhesive polymer matrix. Typically they are presented in the form of a flexible foam or film sheet, coated with a layer of hydrocolloid base and covered with a piece of release paper.

On contact with exudates, hydrocolloids slowly absorb fluid, forming a soft, viscous gel. It facilitates autolytic debridement of slough and necrotic tissue and rehydrates dry wounds by promoting a moist wound environment.

Hydrocolloids are suitable for desloughing and low to high levels of exudating wounds. The frequency of dressing changes should be daily or

Table 1. Function of wound dressing

Dressing Group	**Predominant Function**
Tulle dressing	Protection
Low-adherent contact dressing	Protection
Vapoour permeable films	Protection
Foam dressing	Absorption/Protection
Alginate dressing	Absorption
Hydrogel	Debridement
Hydrocolloid	Absorption/Debridement/Protection
Polysaccharides bead dressing	Absorption/Debridement
Odour-absorbing dressing	Odour control

Table 2. Types of wound and suitable dressing

Types of Wounds	**Recommended dressings**
Lightly exuding wounds	• Foam dressings • Hydrocolloid sheet dressing • Hydrogel dressings • Low-adherent contact dressings • Vapour-permeable film • Tulle-gauze dressing
Moderately exuding wounds	• Alginate dressings • Foam dressings • Hydrocolloid paste and sheets • Hydrogel dressings • Low-adherent contact dressings • Polysaccharide bead dressings
Highly exuding wounds	• Alginates dressings • Foam dressings • Hydrocolloid powder and sheets • Polysaccharide bead dressings
Debriding dry necrotic wounds	• Hydrocolloid dressings • Hydrogel dressings
Debriding moist necrotic wounds	• Alginates dressings • Hydrocolloid dressings • Hydrogel dressings • Polysaccharide bead dressings

alternate days during the early stage of treatment, reducing to weekly with healing progresses.

Examples: Relicare Ultra (Smith & Nephew)
Comfeel (Coloplast)

ix) Polysaccharide bead dressings

Polysaccharides dressings are made from polysaccharides that have been chemically modified and formed into beads or granules. When placed upon a wound, exudate is rapidly taken up by capillary action into the small spaces between the beads. The beads then absorb some of the water and low molecular weight material and swell. Bacteria and cellular debris can also be transported away from the wound surface.

Polysaccharide bead dressings should only be used on exuding sloughy or necrotic wounds e.g. leg ulcers, pressure sores, surgical wounds. They can also be used on infected wounds. The dressing should be discontinued once the wound bed has been fully debrided, as dextranomer can cause discomfort when applied to clean granulation wounds.

Examples: Debrisan (Pharmacia)
Iodosorb (Smith & Nephew)

x) Odour-absorbing dressings

Odour-absorbing dressings are a range of low-adherent dressings combined with either activated charcoal cloth or activated carbon. They absorb the odoriferous chemicals liberated from the wound, before they pass into the air.

The activated charcoal layers of Carbonet are in direct contact with the wound and are able to absorb bacteria and wound toxins. Actisorb Plus contains 0.15% silver, absorbs bacteria and inhibits bacterial growth within the dressing.

Odour-absorbing dressings can be used in conjunction with other dressings. They can be combined with metronidazole gel to control anaerobic bacteria associated with malignant wounds. However, topical metronidazole may induce antibiotic resistance; therefore use should be restricted.

Examples: Carbonet (Smith & Nephew)
Actisorb Plus (Johnson & Johnson)

IV SELECTION FOR DRESSINGS

The selection of dressing products is influenced by a wide range of variables e.g. properties and availability of dressings, patient variables (hypersensitivities, compliance), experience, etc. Also the selection of wound dressings is likely to be more complex as more and more products become available in each generic group of products mentioned above. As inappropriate selection of wound dressings may at best be uncomfortable for the patient, or at worst actively delay wound healing, summarized tables (table 1 & 2) are provided to facilitate our choice in selecting the suitable dressings for different types of wounds. Last but not least, it should be always bear in mind that healing is a dynamic process, and therefore, the properties and performance that are required of a dressing may change as healing progresses.

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Anti-Fungal Agents Old and New: Revisited

Logan, Joyce; Cheng, Man-Loong

2 CE Units

I INTRODUCTION

Some fungi can cause primary infections resulting in diseases in otherwise healthy people. Other types are opportunistic pathogens that reside in the host and only cause infection in immunocompromised hosts. Although there are more than 200,000 fungal species in nature, fewer than 150,000 are known to be human pathogens.

Fungal infections can range from superficial conditions that affect the outermost layers of the skin such as hair and nails to subcutaneous mycoses and infections of the tissue under the skin. More serious invasive systemic mycoses include the involvement of blood and internal organs and these can be potentially lethal.

The incidence of invasive fungal infections has steadily increased over the past two decades and has become a growing medical problem.[1] In part this has been due to the increasing number of patients in whom the immune system has been compromised, mainly due to the increasing prevalence of organ transplantation, the use of cancer chemotherapy and the growing incidence of Acquired Immune Deficiency Syndrome (AIDS). Others who are commonly affected include burn and diabetic patients and also hospitalized patients with indwelling catheters and devices.

Invasive fungal infections are a leading cause of mortality among patients with hematologic malignancies, allogeneic stem cell transplants and solid organ transplants. This article aims to review the current and traditional approaches to the treatment of invasive fungal infections and also discuss the latest advances and emerging therapies.

II FUNGI REVISITED AND THE MAJOR PATHOGENS

Fungi are eukaryotic organisms that represent a separate animal kingdom of life forms, although they are sometimes classified as a subdivision of the plant kingdom. Fungi have nuclei, cell membranes and cell walls, but they lack chlorophyll. Fungi are generally grouped by morphology as either yeasts or moulds.

i) Yeasts

Yeasts are small, round single cells that reproduce by budding and they are the most frequent fungal colonizers and the causes of fungal infections in human. Relatively few yeast species cause human disease. The genus *Candida* is the most common accounting for 60% to 70% of invasive fungal infections in cancer patients and *Cryptococcus neoformans* is another member of the yeast group. There are approximately 200 species in the genus *Candida*. These organisms are present on many plants and several species are also part of the normal flora in human and animal gastrointestinal tracts. Most normal healthy individuals carry one or more *Candida* species but they are only a minor constituent of the gut flora which are predominately bacterial. Historically, *C. albicans* is the most important pathogenic *Candida* species but in recent years non-*albicans* species are representing an increasing proportion of *Candida* blood isolates in oncology as well as general hospital patient population.[2,3,4] In cancer patients, approximately half of *Candida* fungemias today are non-*albicans* including *C. tropicalis, C. glabrata, C. parapsilosis, C. krusei*, etc.[3] The emergence of non-*albicans* species poses a challenge to clinicians because they may be less susceptible to conventional anti-fungal agents.[4,5]

Since *Candida* organisms are normal constituents of the colonizing gut flora, it is not surprising that their portal point of entry to the bloodstream is through the intestinal tract. The intact mucosal barrier is normally impervious to organisms, but many chemotherapeutic regimens damage the mucosa allowing easier penetration of the microorganisms into the portal circulation and their subsequent entry into the systemic circulation.

ii) Moulds

The other major group of fungal pathogens is moulds which consist of filamentous strands called hyphae. *Aspergillus* is the most common mould found in cancer patients, presenting approximately two-thirds of mould pathogens and 15% to 25% of all invasive fungal infections. *Aspergillus* (and other moulds) is not ordinarily found in or on the human body. Instead these airborne organisms are most commonly acquired by inhalation. The most prevalent species are *A. fumigatus* and *A. flavus,* with *A. niger, A. terreus* and others being less common. Other fungal infections that may have formerly been rare have emerged as opportunistic pathogens within the last 20 years. Among these include *Fusarium spp., Acremorium spp, Penicillium spp and Trichoderma spp.*

Although *Aspergillus* and *Candida* cause the majority of severe systemic fungal infections, they are opportunistic pathogens that rarely affect individuals with normal immune system. These fungal infections are often fatal. Despite current therapy, the mortality rates for systemic *Candida* infections can be as high as 30% and the mortality rates for *Aspergillus* infections can be as high as 90%. Due to the urgent need to initiate treatment and the time required to identify the exact nature of the fungal infection, treatment is most frequently initiated empirically. Indeed, because of the very serious nature of systemic fungal infections, prophylaxis is common in certain high-risk patient populations as listed in Table 1.[6]

Table 1. Patient groups in whom prophylaxis against fungal infections is recommended

Types of patients who are indicated for fungal infection prophylaxis:
▼ HIV- infected patients
▼ Neutropenic patients (including patients receiving standard chemotherapy for acute myelogenous leukemia, allogeneic bone-marrow transplants, or high-risk autologous bone-marrow transplants)
▼ Solid-organ transplantation recipients (including patients undergoing liver transplant, and pancreatic transplantation)

Because the human host is not a significant reservoir of organisms, infection caused by most fungal species, except for the genus *Candida*, occurs accidentally in most instances. Thus, fungal infections are usually not contracted by person-to-person contact but rather through exposure to a source in nature or the hospital environment. Recovery of such nonresident organisms in patients suspected of having an infection should therefore be of greater concern than recovery of organisms that are ordinarily part of the natural body flora (e.g. *Candida*).

III CURRENT TREATMENT IN INVASIVE ANTI-FUNGAL THERAPY

i) Amphotericin B - a polyene anti-fungal

Polyenes act by binding to ergosterol (a sterol molecule found in fungal cell membranes), thus increasing membrane permeability and leading to cell leakage and death. Amphotericin B is the only polyene anti-fungal agent used to treat systemic infections. Amphotericin B has a broad spectrum of activity against most species of *Candida* and *Aspergillus* and is used to treat many other types of severe systemic fungal infections.

Amphotericin B is usually given at a dose of 0.25 to 1.5mg/kg/day IV over 2-6hours, depending on the severity of infection and the type of pathogen involved. Although amphotericin B has been the mainstay of therapy for systemic fungal infections, it has many adverse effects including infusion-related (e.g. fever, chills, nausea and vomiting) and dose-related adverse effects (e.g. arrhythmia and electrolyte abnormalities including hypokalemia, hypomagnesemia, hypernatremia and metabolic acidosis). Most importantly, it can reduce glomerular filtration and cause acute renal failure.[7,8,9,10,11,12] It appears that the nephrotoxicity is mediated in part by its direct toxic effect on renal tubular cells resulting in acute tubular necrosis,[13] and in part by its vasodilating effect.[13,14,15,16,17] There is no specific treatment available to reverse acute renal failure although intravenous loading with 500-1000mL of normal saline before infusion of amphotericin B has been used with some success as a prophylactic measure.[18,19,20] The acute renal failure associated with amphotericin B is often dose-dependent and duration-dependent. Several risk factors have been identified and these are tabulated in Table 2.[21] Infusion-related adverse effects can be effectively suppressed by use of hydrocortisone as these adverse effects are mostly cytokine-mediated.[22] The use of test dose (1mg infused over 20-30 minutes) to identify patients at risk of acute allergic reaction has been advocated; however, the risk of such reaction is rare.[23]

Table 2. Factors that increase the risk of amphotericin B-associated nephrotoxicity

Factors that increase the risk of amphotericin B- associated nephrotoxicity:
▼ Male gender
▼ Increased body weight
▼ Chronic renal disease
▼ Previous/concomitant treatment with other nephrotoxic agents (e.g. cyclosporin, aminoglycosides)

The development of lipid formulations of amphotericin B was also an attempt to reduce the toxicities associated with the drug. There are now three lipid formulations available globally, including amphotericin B lipid complex, amphotericin B chloesteryl sulphate (also known as amphotericin B colloidal complex) and liposomal amphotericin B. However, only the last two are available in Hong Kong market. Although these drugs appear to be less nephrotoxic,[24] their efficacies relative to amphotericin B have not been demonstrated for invasive fungal infections such as Aspergillosis. The dosage of the lipid-based formulations is 3-6mg/kg daily, different from that of conventional amphotericin B. These lipid-based formulations are available only as injectables and are preferentially taken up by reticuloendothelial organs - specifically the lungs, liver and spleen. With these lipid formulations, higher doses of amphotericin B can be used and patients typically experience less nephrotoxicity. Patients who are intolerant to conventional amphotericin B may be switched to a lipid-based formulation.

ii) Azoles - Fluconazole as the representative and voriconazole as the new comer

Introduction of this class of drugs has led to a significant advancement in the treatment of fungal infections. Azoles act by inhibiting the cytochrome P450 dependant enzyme lanosterol 14 alpha- demethylase. This enzyme is involved in the conversion of lanosterol to ergosterol. Azoles can be classified into two groups; namely triazole (including itracolazole and fluconazole) and imidazole (namely ketoconazole). Fluconazole is considered to be a more suitable candidate for systemic infections due to its higher bioavailablilty, higher peak plasma concentration, less protein binding and higher penetration to the cerebrospinal fluid.[25] Azoles have a broad spectrum of activity covering common pathogens (e.g. *Candida* species, *Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum*) although it is not active against *Aspergillus* (except itracolazole). They offer an excellent safety profile with no nephrotoxic potential and are available in both oral and intravenous formulations. Gastrointestinal side effects such as nausea and vomiting, diarrhea have been reported. Skin rash can also occur. The most severe side effect is hepatotoxicity.

However, azoles are not without limitations. The main concerns are the emergence of drug resistant pathogens especially *Candida* species, and their potential to cause drug interactions. The more common drug interactions are listed in Table 3.[25]

Table 3. Drug interactions involving oral azole anti-fungal drugs

Type on Drug Interaction	**Drug involved**
Decreased plasma concentration of azole	
Decreased absorption of azole	Antacids; H_2 receptor antagonists; Sucralfate; Omeprazole; Didanosine (oral)
Increased metabolism of azole	Isoniazid; Rifampin; Phenytoin; Carbamazepine; Phenobarbital
Increased plasma concentration of co-administered drug	
	Alprazolam; Chlordiazepoxide; Cyclosporine; Digoxin; Felodipine; Indinavir; Loratadine; Lovastatin; Midazolam; Nifedipine; Nortriptylline; Rifabutin; Ritonavir; Saquinavir; Sulphonylureas; Tacrolimus; Triazolam; Warfarin; Zidovudine

Voriconazole is a recently introduced triazole anti-fungal drug. It is structurally related to fluconazole and its development was an attempt to improve the activity of fluconazole. Voriconazole exhibits fungistatic activity *in vitro* against the *Candida* spp.,[26] and fungicidal activity against the *Aspergillus* species.[27] Voriconazole is available in both oral and IV formulations. Its major side effects include hepatotoxicity and visual adverse effects. The US Food and Drug Administration (FDA) recently approved it for treatment of invasive aspergillosis, oesophageal candidiasis and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium spp.* However, there are still drawbacks for voriconazole as it is metabolized by CYP2C19, 2C9 and 3A4, thus drug interactions are possible and it was found to prolong QT interval in animal studies.[28]

iii) Caspofungin - member of the novel Echinocandin class

Echinocandin is a cyclic lipopeptide, which specifically inhibits fungal 1,3-β-D glucan synthesis. The glucose homopolymer B-(1,3)-D-glucan is an essential component of the fungal cell wall. Inhibition of 1,3-β-D glucan synthesis results in defective cell wall polymerization and renders the fungal organism susceptible to lysis and cell death.[29] Caspofungin is the first agent in the Echinocandin class of anti-fungal drugs.

Studies have demonstrated its broad spectrum of activity. It exhibits both *in vitro* and *in vitro* efficacy against a wide range of fungi and yeasts such as *Aspergillus* and *Candida spp.* including the azole-resistant strains.[30] The US FDA has approved Caspofungin for invasive aspergillosis in patients who are refractory to or intolerant to other therapies (i.e. amphotericin B, lipid formulations of amphotericin B and/or itraconazole), and also for oesophageal candidiasis. However, the drug has not been studied as initial therapy for invasive aspergillosis.[31] The drug is given once daily by intravenous route and has to be infused over one hour. For invasive aspergillosis, a loading dose of 70mg is administered on Day 1 followed by 50mg daily on subsequent days. Loading dose is not required for treatment of oesophageal candidiasis.[31] Dosage adjustment is not necessary for renal impairment, but in patients with moderate hepatic insufficiency, dosage reduction is required.[32]

A complete or partial response to caspofungin was seen in 41% of immunocompromised adults with invasive aspergillosis who did not respond to or tolerate other anti-fungal agents in a non-comparative multicentre study. The duration of therapy in this trial ranged from one to 162 days.[33] Caspofungin 50mg or 70mg daily has demonstrated superior efficacy compared to amphotericin B in terms of the rate of endoscopically verified clinical success (74% or 89% vs. 63%) in patients with oropharyngeal candidiasis.[34] Adverse events were reported in 13.8% of study patients. The most common clinical adverse effects were fever, infusion-related venous side effects, nausea and vomiting.[33]

Studies conducted in healthy volunteers indicated that its pharmacokinetic profile was not altered by co-administration of amphotericin B, mycophenolate mofetil and tacrolimus. Moreover, the active metabolites of mycophenolate mofetil were not altered by co-administration of caspofungin.[31]

The plasma concentration and area-under-curve (AUC) of tacrolimus was modestly reduced by about 20% when co-administered with caspofungin. Thus, the plasma concentrations of tacrolimus should be monitored in patients receiving both drugs.[34]

The concomitant use of caspofungin and cyclosporin is currently not recommended unless the potential benefit outweighs the potential risk to the patient. Cyclosporin increased

the AUC of caspofungin by about 35% although the plasma concentration of cyclosporin was not altered by caspofungin.[34] Increase in alanine aminotransferase concentrations has been reported in normal subjects during co-administration with cyclosporin.[32]

IV CONCLUSION

The advancement of anti-fungal agents has greatly improved the clinical outcomes of patients who have fungal infection. While a number of anti-fungal agents are now available, the treatment response rate remains unsatisfactory. The introduction of voriconazole and caspofungin has provided more options in the management of fungal infections. Other new agents are also undergoing late phase of clinical trials and will be ready for marketing in the near future. These include the azoles, ravuconazole (BMS-207147) and posaconazole (SCH-56592); and the new echinocandin candidates, micafungin (FK463) and anidulafungin (LY-303366). Results from clinical studies are awaited in order to determine the roles of these newer agents in clinical practice.

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Great News ....

Continuing Education Units (CEUs) for Authors of Articles in the HKPJ. At the most recent meeting of the Pharmacy Central Continuing-education Committee (PCCC), it was decided that CEU would be awarded to authors of articles published in the HKPJ. For each issue, the Editorial Committee, led by the Managing Editor, will choose an article from all the published articles in that issue, for PCCC to use for CE purposes. The author(s) is(are) responsible for setting questions for the approved CE article. Primary authors are entitled to receive 6 CEUs and other co-authors of the same CE article are entitled for 4 CEUs granted by PCCC. For details on how to get CEU, please refer to the article named "PCCC Continuing Education Units (CEU) Accrediting System" [HKPJ 2002;11(2):79-80].

Great news to boost the professional standard and recognition of the contributions to the HKPJ!

Questions for Pharmacy Central Continuing Education Committee Program

1. Which of the following is a member of the yeast group?

A. *Aspergillus* spp.
B. *Penicillium* spp.
C. *Fusarium* spp.
D. *Candida* spp.

2. Which of the following measure is generally not practiced when regular amphotericin B is administered?

A. Usual dose of amphotericin B is administered as an IV push in 2-5 minutes
B. A test dose is given to rule out possible allergic reaction
C. 500mL Normal saline is infused prior to administration of amphotericin B
D. Hydrocortisone is administered as a pre-medication.

3. Which of the following Candida organism is generally the most sensitive to amphotericin B therapy?

A. *Candida albicans*
B. *Candida glabrata*
C. *Candida krusei*
D. *Candida tropicalis*

4. HM is a 38-year-old male with creatinine clearance of 25mL/min. He is receiving amphotericin B and gentamicin therapy for sepsis. Which of the following is NOT a risk factor that may predispose HM to amphotericin B nephrotoxicity?

A. Male gender
B. Young adult
C. Renal impairment
D. Concurrent use of gentamicin

5. Which of the following anti-fungals is generally not effective for Aspergillus infections?

A. Amphotericin B
B. Fluconazole
C. Itraconazole
D. Caspofungin

2 CE Units

Anti-Fungal Agents Old and New: Revisited

6. Which of the following azoles does not have a parenteral preparation?

A. Fluconazole
B. Itraconazole
C. Ketoconazole
D. Voriconazole

7. TH is a bus captain and presented to your pharmacy. She had a runny nose and requested some medications for relief. During patient interview, you noticed that she has just got a dose of 150mg fluconazole stat for her vaginal candidiasis this morning. Among the following agents, which agent would be the most appropriate for her?

A. Cetirizine
B. Chlorpheniramine
C. Loratadine
D. Terfenadine

8. Which of the following situations would you consider the use of caspofungin therapy most appropriate?

A. A male adult presenting with oesophageal candidiasis recently without previous treatment.
B. A male adult presenting with invasive aspergillosis of pulmonary origin, who did not respond to previous treatment with liposomal amphotericin B.
C. A lady presenting with vaginal candidiasis recently with no dissemination.
D. A lady presenting with invasive cryptococcal infection who did not respond to previous treatment with fluconazole.

9. What is the recommended dosage of caspofungin in a 32-year-old, 60kg adult with an estimated creatinine clearance of 40mL/min and a diagnosis of invasive aspergillosis refractory to amphotericin B treatment?

A. Caspofungin is contra-indicated in patients with an estimated creatinine clearance of <50mL/min.
B. Patient should be given caspofungin 50mg daily.
C. Patient should be given a loading dose of 70mg on Day 1 and then maintained on 50mg daily.
D. Patient should be given caspofungin 70mg daily.

10. TF, a 35-year-old male, is a kidney transplant recipient who received the kidney graft 2 days ago and is now staying in the surgical ward, currently on cyclosporin and prednisolone. Today, invasive aspergillosis is diagnosed and the doctor wants to initiate caspofungin as amphotericin B has nephrotoxic side effect. All of the following biochemical markers should be closely monitored except:

A. Liver function tests
B. Renal function tests
C. Serum cyclosporin level
D. None of the above

Review and Update on the Management of Hypertension

Wong, Sammas

I OVERVIEW

Hypertension is defined as an elevated value of systolic blood pressure (SBP)≥140mmgHg or diastolic blood pressure (DBP) ≥90mmgHg.[1] The disease often goes undetected because most people with hypertension are asymptomatic but unfortunately improper management of such can lead to heart disease, stroke, renal failure and blindness. According to the Department of Health, cardiovascular diseases (CVD) including hypertensive disease have been ranked the second as the leading cause of death in Hong Kong over the past two decades. In particular, the prevalence of cardiovascular death was 73.2 per 100,000 in the year 2002.[2] A local survey conducted a decade ago demonstrated that among 1,513 Chinese subjects of working age, the prevalence of hypertension was 26% and 7% in those with and without diabetes, respectively.[3] Another local prescription survey showed that 24.5% and 47.1% of patients were prescribed antihypertensive drugs in a general outpatient clinic and a medical/geriatric specialist clinic, respectively.[4]

In the United States, hypertension affects approximately 50 million individuals which accounts for 25% of her adult population.[5] The International Collaborative Study of Cardiovascular Disease in ASIA (InterASIS), conducted in 2000-2001, revealed that 27.2% of the Chinese adult population (129,824,000 persons) aged 35 to 74 years had hypertension.[6] The relationship between blood pressure (BP) and risk of CVD is consistent and independent of other risk factors. The higher the BP, the greater the risk of myocardial infarction, heart failure (HF), stroke and renal diseases.[7] A local study concluded that hypertension is an important and perhaps the most determining etiological factor for HF.[8] Therefore, appropriate management of patients with hypertension is essential to reduce the risk of CVD and also minimize health care expenses.

II NATIONAL AND INTERNATIONAL CLINICAL GUIDELINES

Following the establishment of the National Heart, Lung and Blood Institute (NHLBI) in the United State, the first report of the Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure was published in 1977. Since then reports have been issued approximately every 4 years to serve as both expert consensus and evidence-based guidelines. In addition to this committee, the International Society of Hypertension (ISH) and the World Health Organization (WHO) have also issued joint recommendations from a more international perspective. The JNC and WHO/ISH were in agreement with respect to choice of drugs for initial therapy until 1993 when the WHO/ISH recommendations deviated from those of the JNC.

The most updated JNC report was the JNC 7 published in 2003.[9] The WHO/ISH is now reviewing the hypertension guideline based on her 1999 version[1] and this new update is currently undergoing peer review which will be due for publication and wider circulation in a few months' time.

Meanwhile, the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) have their joint hypertension guideline published in 2003[10] in response to the WHO/ISH 1999 version that suggested regional experts to draw up recommendations specifically directed towards the management of patients in their own regions.

III ETIOLOGY AND PATHOPHYSIOLOGY

The vast majority of hypertensive patients do not have any identifiable cause (termed as Primary or Essential hypertension) but familial clustering probably exists.[11] Only less than 10% of patients have certain definite causes (termed as Secondary hypertension) such as drug-induced BP elevation [Table 1]. Other possible causes are summarized in Table 2.

A clear understanding of the contributing factors involved in the development of primary hypertension facilitates the rational use of appropriate antihypertensive drug therapy. These include the abnormality of renin-angiotensin-aldosterone system and neuronal mechanism; disturbance of sodium, calcium and natriuretic hormones; defective peripheral autoregulation, and presence of hyperinsulinemia.[12]

IV BP MEASUREMENT AND CLINICAL EVALUATION

Patient should be seated for at least five minutes in a chair with arm supported at heart level before BP is measured. An appropriate-sized cuff bladder encircling at least 80% of arm should be used and at least two measurements need to be recorded.[13] Ambulatory BP monitoring, on the other hand, is found to correlate better with target organ damage (TOD) than clinic measurements and is useful for evaluation of efficacy of antihypertensive agents and hypotensive episodes associated with their use.[14] Moreover, BP values normally reduce by 10% to 20% during sleep in most individuals and absence of nocturnal reduction may indicate an increased risk of cardiovascular events.[9]

Besides BP values, routine laboratory tests (ECG, urinalysis, blood glucose, electrolytes, hematocrit, lipid panel, renal function); complete physical examination; and assessment of family history are essential for differential diagnosis.[15] Additionally, the following three factors should be evaluated before treatment initiation. They are: 1) presence of other

Table 1. Drug-Induced Hypertension [28]

Adrenocorticosteriods
Alcohol
Appetite suppressants (ephedra, MaHuang, caffeine)
Cocaine; amphetamines
Cyclosporine; Tacrolimus
Erythropoietin
Estrogen (especially for use as oral contraceptive)
Licorice
Monoamine oxidase inhibitors
Non-steroidal anti-inflammatory drugs
Sympathomimetics (e.g. pseudoephedrine, phenylpropanolamine)
Tricyclic antidepressants
Venlafaxine

cardiovascular risk factors, 2) presence of TOD and associated clinical conditions (ACC), and 3) the possibility of identifiable causes for high BP [Table 2].[9,10]

V TREATMENT

1) Goal

The primary goal of management of hypertension is to reduce the long-term risk of cardiovascular morbidity and mortality. It is recommended that SBP/DBP be lowered to at least <140/90mmHg in the general population. For those with diabetes mellitus or renal diseases the goal is <130/80mmHg.[1,16] SBP was found to correlate with cardiovascular risks more than DBP especially for those aged 50 or older.[17,18]

Table 2. Factors for consideration when evaluating patients with documented hypertension[1,9,10]

Major Risk Factors of hypertension
✦ Cigarette smoking
✦ Dyslipidemia
✦ Diabetes
✦ Obesity* (BMI[19] >24)
✦ Sedentary lifestyle
✦ Microalbuminuria or estimated glomerular filtration rate <60ml/min
✦ Men >55years or Women >65years
✦ Family history of premature cardiovascular diseases (men >55years or women >65years)
Target Organ Damage (TOD)
✦ Left ventricular hypertrophy
✦ Proteinuria 30-300mg/day or serum creatinine (SCr)1.2-2.0mg/dL
✦ Ultrasound or radiological evidence of atherosclerosis
✦ Narrowing of retinal arteries
Associated Clinical Conditions (ACC)
✦ Cerebrovascular disease (stroke; transient ischemic attack)
✦ Heart disease (angina; myocardial infarction)
✦ Renal disease (diabetic nephropathy; renal failure with SCr>2mg/dL; proteinuria >300mg/day)
✦ Peripheral vascular disease
✦ Advanced retinopathy (hemorrhage or exudates; papilloedema)
Identifiable Causes of Hypertension
✦ Drug-induced or drug-related (Table 1)
✦ Renal disease (renoparenchymal disease; renovascular disease)
✦ Primary aldosteronism
✦ Sleep apnea
✦ Cushing's Syndrome
✦ Coarctation of aorta
✦ Pheochromocytoma
✦ Thyroid or parathyroid disease

**BMI (Body Mass Index) = body weight(kg) / height^2 (m^2)*

Table 3. Classification of the severity of hypertension and prognosis quantification[1,9,10]

		Blood Pressure (mmHg) and Classification				
		SBP 120-129 and DBP 80-84	SBP 130-139 or DBP 85-89	SBP 140-159 or DBP 90-99	SBP 160-179 or DBP 100-109	SBP ≥ 180 or DBP ≥ 110
Classifying Authorities	JNC 7	Prehypertension		Stage 1	Stage 2	
	WHO/ISH & ESH/ESC	Normal	High Normal	Grade 1	Grade 2	Grade 3
Risk Level stratification to quantify prognosis*	No other risk factors	Low	Low	Low	Moderate	High
	1-2 risk factors	Low	Low	Moderate	Moderate	Very high
	3 or more risk factors or TOD or diabetes	Moderate	High	High	High	Very high
	ACC	High	Very high	Very high	Very high	Very high

TOD=Target Organ Damage; ACC=Associated Clinical Conditions; SBP=Systolic blood pressure; DBP=Diastolic Blood Pressure;
**Only applicable to classification by WHO/ISH & ESH/ESC*
If SBP >140mmHg and DBP <90mmHg, it is classified as Isolated Systolic Hypertension

2) Classification and treatment algorithms[1,9,10]

The JNC, WHO/ISH and ESH/ESC all provide detailed classification and treatment strategies for hypertension. In general, lifestyle measures and correction of other reversible risk factors should always accompany pharmacological treatment. Table 3 illustrates the BP classification defined by each of the above authorities. The WHO/ISH and ESH/ESC quantify the prognosis of patients with hypertension by taking into account BP values and the presence of various risk factors. The JNC 7 classifies subjects with SBP 120-139mmHg or DBP 80-89mmHg as "pre-hypertensive" and recommends lifestyle modification for prevention of CVD. It also combines Stage 2 ("Stage" is equivalent to "Grade" as used by WHO/ISH and ESH/ESC) and Stage 3 hypertension as opposed to the JNC 6 guidelines. Figure 1 shows the simplified treatment algorithm for hypertension. The WHO/ISH and ESH/ESC guidelines take into account both the BP levels and other cardiovascular risk factors when implementing drug therapy while the JNC 7 bases treatment decisions solely on BP levels. Additionally, patients should be followed up regularly to ensure BP goals are reached and complications are minimized.

3) Non-drug treatment

Lifestyle modifications are essential for BP lowering in all individuals in the first place. These include weight reduction for those who are overweight, dietary sodium restriction, adequate and suitable physical activities, as well as moderation of alcohol consumption [Table 4].

Table 4. Lifestyle modifications to control hypertension[1,9,10]

Modification	Advice	BP reduction (mmHg)
Weight reduction	Maintain BMI[19] <24	5-20 / 10kg weight loss
Increased physical activity	Perform modest level of aerobic exercise on regular basis, e.g., brisk walk or swim for 30 minutes most days of the week	4-9
Moderate alcohol intake	Men limit consumption to no more than 30ml ethanol (24oz beer; 10oz wine; 3oz 80-proof whiskey) Women limit consumption to half of the limit for men	2-4
Dietary sodium restriction	Reduce intake to less than 6g sodium chloride / day (= 1 teaspoon)	2-8
Adopt DASH[20] eating plan	Maintain a diet rich in vegetables, fruits and low fat dairy products; reduce saturated and total fat	8-14
Smoking cessation and relief of psychological stress	Smoking cessation can prevent cardiovascular complications of hypertension; alleviation of stress reduce BP fluctuation and improve compliance	No data

DASH = Dietary Approach to Stop Hypertension; BP = blood pressure; BMI = body mass index

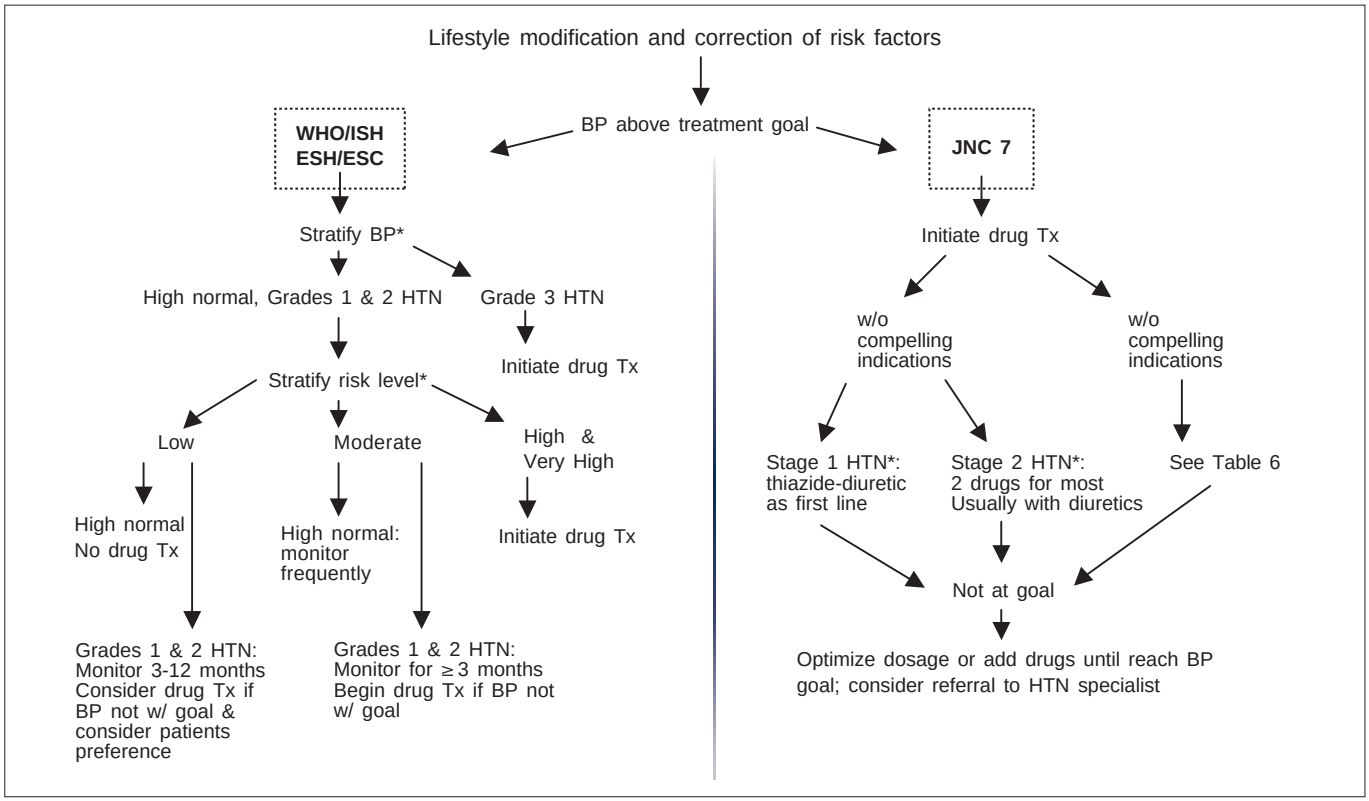

Figure 1. Simplified treatment algorithm of hypertension[1,9,10]

*refer to Table 3; BP = blood pressure; HTN = hypertension; w/ = within; w/o = without; Tx = treatment

4) Pharmacological management

Numerous studies have documented the efficacy of different types of pharmacological agents in lowering BP and reducing the risks of hypertension-related complications.[21,22] These agents are described as follows. The recommended dosage of individual agents, and their respective compelling/possible indications and contraindications are summarized in Table 5.

a) Diuretics

Diuretics work initially by reducing plasma volume and, in the long term, decrease BP levels by lowering peripheral vascular resistance. They are inexpensive, effective and generally well tolerated. They have also been studied extensively and proven to be effective in preventing stroke and major CVD.[23,24] Many of the unwanted side effects such as potassium depletion, glucose intolerance, impotence and ventricular ectopic beats[25] can be reduced by using lower dose of diuretics and use of potassium-sparing diuretics.

b) Beta-blockers

Beta-blockers blunt heart rate and contractility (hence reduce cardiac output), alter baroceptor reflex sensitivity, block peripheral adrenoceptors and may also depress plasma renin secretion. [26] They are divided into the non-cardioselective or cardioselective subtypes with the latter preferred for those with diabetes. Common side effects include bradycardia, bronchospasm, cold extremities; and abrupt cessation of treatment may precipitate acute coronary syndromes. Some beta-blockers are more water soluble (e.g. atenolol, nadolol); thus have less side effects related to the central nervous system but their use requires dosage adjustment in renally impaired patients.

c) Angiotensin converting enzyme inhibitors (ACEIs)

ACEIs directly inhibit the conversion of angiotensin I to angiotensin II by the angiotensin-converting enzyme, subsequently reducing vasoconstriction and aldosterone secretion and finally lowering BP. They are particularly indicated for hypertension in insulin-

Table 5. Oral Antihypertensive Agents[1,9,10]

Class of Drugs	Usual dosage Total mg/day (daily frequency)	Indications		Contraindications	
		Compelling	Possible	Compelling	Possible
Diuretics		• Heart Failure • Elderly • Systolic HTN	• Diabetes • Osteoporosis	• Gout • Hyperkalemia (K+ sparing) • Renal failure	• Dyslipidemia • Pregnancy
(thiazide): HCTZ Indapamide Metolazone	 12.5-50 (1) 1.25-2.5 (1) 2.5-5 (1)				
(K+ sparing): Amiloride Spironolactone Triamterene	 5-10 (1) 25-50 (1) 50-100 (1)				
(loop) Frusemide Bumetanide	 20-80 (2-3) 0.5-2 (2)				
Beta-blockers		• Angina • Post MI • Tachycardia • Migraine	• Diabetes • Heart failure	• Asthma • COPD • Heart block	• Dyslipidemia • Athletes • PVD
Atenolol Bisoprolol Metoprolol Nadolol Propranolol	25-100 (1) 2.5-10 (1) 50-100 (1-2) 40-120 (1) 40-160 (2)				
ACEIs		• Heart failure • LV dysfunction • Post MI • Diabetes • Nephropathy	–	• Pregnancy • Bilateral renal artery stenosis • Hyperkalemia	–
Benazepril Captopril Enalapril Fosinopril Lisinopril Perindopril Ramipril	10-40 (1-2) 25-150 (1-3) 5-40 (1-2) 10-40 (1-2) 5-40 (1-2) 4-8 (1-2) 1.25-20 (1-2)				
ARBs		• ACEI cough	• Heart failure	• Pregnancy • Bilateral renal artery stenosis • Hyperkalemia	–
Candesartan Losartan Irbesartan Telmisartan Valsartan	8-32 (1) 25-100 (1-2) 150-300 (1-2) 20-80 (1) 80-320 (1)				
CCBs		• Angina • Elderly • Systolic HTN (dihydropyridine)	• PVD	• Grade 2-3 Heart block (diltiazem, verapamil)	• Congestive heart failure (except amlodipine & felodipine) • Tachycardia
(dihydropyridine) Amlodipine Felodipine Nifedipine* Nicardipine	 2.5-10 (1) 2.5-20 (1) 30-60 (1-2) 60-120 (2)				
Diltiazem Verapamil	120-360 (2) 90-360 (1-2)				
Peripheral alpha1 blocker		• Prostatic hypertrophy	• Glucose intolerance • Dyslipidemia	• Orthostatic Hypotension	• Congestive heart failure
Doxazosin Prazosin Terazosin	1-16 (1) 2-20 (1-3) 1-20 (1-2)				
Central alpha2 agonist		–	–	–	–
Methyldopa	250-1000 (2-3)				
Direct Vasodilator		–	–	–	–
Hydralazine Minoxidil	25-100 (2) 2.5-80 (1-2)				

ACEIs = Angiotensin converting enzyme inhibitors; ARBs = Angiotensin 2 receptor blockers; CCBs = Calcium channel blockers
COPD = chronic obstructive pulmonary disease; HTN = hypertension; K+ = potassium; LV = left ventricular; MI = Myocardial infarction; PVD = peripheral vascular disease.
** sustained release formulation only*

dependent diabetics with nephropathy.[27] The first dose should preferably be given at bedtime especially in those receiving diuretic therapy. However, ACEIs are associated with reduction in aldosterone level and subsequently hyperkalemia, and accumulation of bradykinin resulting in dry cough in predisposed patients.[28]

d) Angiotensin II receptor blockers (ARBs)

ARBs modulate the renin-angiotensin-aldosterone system by directly blocking the angiotensin II receptor. It has been postulated that due to their similar mechanisms of actions, ARBs and ACEIs should produce similar clinical outcomes.[29] Nevertheless, they do not affect bradykinin metabolism thus have the advantage of not causing persistent dry cough. Due to their relatively high cost and inadequate clinical studies of their use in hypertension, many clinicians reserve ARBs as second- or third-line agents in patients who suffer cough from ACEIs.[30]

e) Calcium Channel Blockers (CCBs)

CCBs lower BP by relaxation of vascular smooth muscles and the resulting coronary and peripheral vasodilatation. Dihydropyridine CCBs are valuable for isolated systolic hypertension in the elderly when a low-dose thiazide is contraindicated or not tolerated.[28] The STONE study demonstrated that nifedipine significantly reduced the risk of adverse clinical outcomes (stroke, arrhythmia) vs placebo in elderly hypertensives.[31] However, non-dihydropyridine group of CCBs can block AV node, decrease cardiac contraction and are thus contraindicated in HF or heart block. Concurrent therapy of verapamil with beta-blocker is best avoided due to their prominent depressive effect on ventricular contractility when used together.[25] Tachycardia, flushing, ankle edema and constipation (with verapamil) are the most common undesirable effects of CCBs. The use of long-acting CCBs (e.g. amlodipine, felodipine, modified release nifedipine) is recommended since they improve compliance and minimize BP variability, thus providing greater protection from developing TOD and major CVD.[32] On the other hand, the use of immediate-release nifedipine should be avoided in hypertensive crisis (see below) since it has been associated with cerebrovascular ischemia, acute myocardial infarction, heart block and sinus arrest. The possible mechanism of such adverse events are the excessive and rapid BP drop that results in reflex tachycardia, reduced cardiac output and a coronary steal phenomenon.[28]

f) Peripheral alpha1 blockers

Peripheral alpha1 blockers inhibit uptake of catecholamines in smooth muscle and cause vasodilatation. Evidence in favor of their use in hypertension is scanty compared to other classes of antihypertensive agents. Meanwhile, the doxazosin arm in the ALLHAT trial[23] was stopped prematurely before study end because patients allocated to this arm were found to have 25% higher rate of cardiovascular events and 2-fold higher risk of HF compared to the thiazide diuretic arm. Nevertheless, they are useful for combination therapy as suggested in the JNC 7. Again, due to drastic drop in BP upon initiation, the first dose should be introduced at bedtime with appropriate patient counseling.

g) Central alpha2 agonists

Central alpha2 agonists decrease sympathetic outflow from the vasomotor centre of the brain and also lower peripheral vascular resistance and cardiac output. Their use is commonly associated with peripheral edema but other side effects such as dry mouth and sedation are minimal if a lower dose is used. Due to cost concern, methyldopa (usually used with diuretics to counteract the fluid retention) is in fact the most popular choice of antihypertensive agent prescribed in general outpatient clinics in Hong Kong according to a recent survey.[4]

h) Arterial Vasodilators

Arterial vasodilators such as hydralazine and minoxidil are considered the last resort for treatment of hypertension and should be used only as part of combination therapy as they can induce reflex tachycardia and significant fluid retention.[28]

5) Drugs of Choice

When pharmacological treatment is indicated, the primary treatment outcome is to lower BP per se. A number of large-scale clinical trials have demonstrated that most patients, especially the elderly, require two or more antihypertensive medications to achieve the BP goal. In the HOT study[33], a randomized and controlled clinical trial that involved more than 18,000 subjects (mean age 61.5 years) from 26 countries, monotherapy was shown to be successful in only 25-40% of patients with Grades 2 or 3 hypertension (as defined by WHO/ISH). In the PROGESS[34] study, which involved more than 6,000 participants (mean age 64 years) from Asia, Europe and Australia, combination therapy with perindopril and indapamide was found to produce larger BP reduction and better clinical outcomes compared to monotherapy with perindopril in patients in whom secondary prevention of stroke was indicated.

For the choice of antihypertensive agents, the JNC 7 referred to the findings of the recently published ALLHAT[23] study. The ALLHAT study was the largest randomized, double-blind, active-controlled, hypertension study that compared a thiazide diuretic (chlorthalidone) with the newer antihypertensive drugs as first-choice BP lowering treatment. It was suggested that thiazide-type diuretics should be the drug of choice for initial therapy of hypertension unless it is intolerable or contraindicated. When hypertensive patients need more than one drug, diuretics should generally be part of the regimen. The JNC 7 also states that when BP is >20/10mmHg above treatment goal, consideration should be given to initiate therapy with two drugs, but special cautions should be given to those at risk of orthostatic hypotension such as the elderly or patients with diabetes or autonomic dysfunction.

The ESH/ESC guidelines are based on much the same evidence as the JNC 7 but are less rigid regarding the choice of drugs. The selection of agents should be individualized based on patient's preference, concomitant TOD or ACC, and the costs of agents. According to baseline BP levels and the presence or absence of complications, it is reasonable to initiate treatment using low dose combination therapy. The use of two drugs at the beginning may potentially expose the patients to unnecessary agents but there are several advantages. Firstly, the use of two drugs with different mechanisms of actions may reduce BP more effectively. Secondly, each of the two drugs may be used at a lower dose resulting in less drug-related side effects. Finally, the use of fixed, low-dose combination in form of a single tablet may optimize patient compliance. However, combination of agents with similar mechanism of actions or side effect profiles should be avoided. Figure 2 illustrates some of these effective combinations proposed by the ESH/ESC.

6) Special consideration for treating hypertension in certain population groups

a) Pregnant and breast-feeding women

Non-drug therapy is the preferred

approach to manage hypertension in pregnant women, although pharmacological treatments should be considered if there is evidence of TOD or BP >150/100mmHg.[35] Methyldopa, beta-blockers (labetalol) and arterial vasodilators (hydralazine) are considered to be safe during pregnancy and lactation while ACEIs and ARBs are contraindicated.[25] Pre-eclampsia that occurs after the 20th week of gestation may develop into hypertensive emergency in which parenteral antihypertensive agents may be required.

b) Children and adolescents

The definition of hypertension in this population is based on the >95th percentile adjusted for age, height and sex.[36] Lifestyle intervention and resolving identifiable causes of hypertension are of particular importance. The drugs of choice are similar to those of adult population. Dosage should be adjusted according to clinical efficacy. Both ACEIs and ARBs are not recommended for sexually active girls.

c) Elderly

The benefits of antihypertensive agents in older patients with systolic-diastolic or isolated systolic hypertension are well established.[37, 38] A recent meta-analysis published in Lancet[39] concluded that the risks of cardiovascular events were significantly reduced by antihypertensive treatments in individuals aged 80 years and over. The treatment principles are essentially the same as the general guidelines but lower initial doses and multiple agents are recommended in this patient group.

d) Ischemic heart disease

Beta-blockers and ACEIs are recommended for patients with acute coronary syndromes (unstable angina or myocardial infarction) while beta-blockers and long-acting CCBs should be considered in patient with stable angina. Concomitant aspirin and intensive lipid management are also warranted.[9,23]

e) Heart failure

Diuretics and ACEIs should be initiated in patient with HF regardless of the severity of left ventricular (LV) dysfunction. The National Institute of Clinical Excellence in the United Kingdom (UK) recommends the use of beta-blockers following diuretics and ACEI therapy. Bisoprolol and carvedilol are licensed for treatment of HF in UK but other beta-blockers can also be used if they have been previously utilized for concomitant condition such as hypertension. Beta-blockers should be introduced in a "start low, go slow" manner and assessment of heart rate, BP and patient's clinical status are required during each titration. For patients who remain symptomatic despite optimal treatment as described above, low-dose spironolactone (25-50mg daily) should then be prescribed under the advice of cardiologists. Monitoring of serum potassium and renal function is essential especially with the concurrent use of ACEIs in this group of patients.[40]

f) Diabetes and renal diseases

Two or more antihypertensive agents are usually necessary to achieve the BP goal of <130/80mmHg for this group of patients.[41] Low-dose thiazides, beta-blockers, dihydropyridine CCBs, ACEIs and ARBs are beneficial in reducing the incidence of stroke and CVD in patients with diabetes. ACEIs and ARBs reduce proteinuria and confer renoprotective effects. While the use of ACEIs or ARBs may cause an initial acute renal deterioration, an increase in serum creatinine concentration by up to 35% above baseline is acceptable for renally impaired subjects unless hyperkalemia develop.[42]

g) Hypertensive crisis

Patients with BP >220/130mmHg (malignant hypertension) deserve immediate medical attention. For patients without TOD, treatment can be initiated by oral route with beta-blockers or long-acting CCBs, and parenteral therapy is indicated if TOD occurs. BP should be reduced gradually with careful monitoring to avoid acute ischemia.

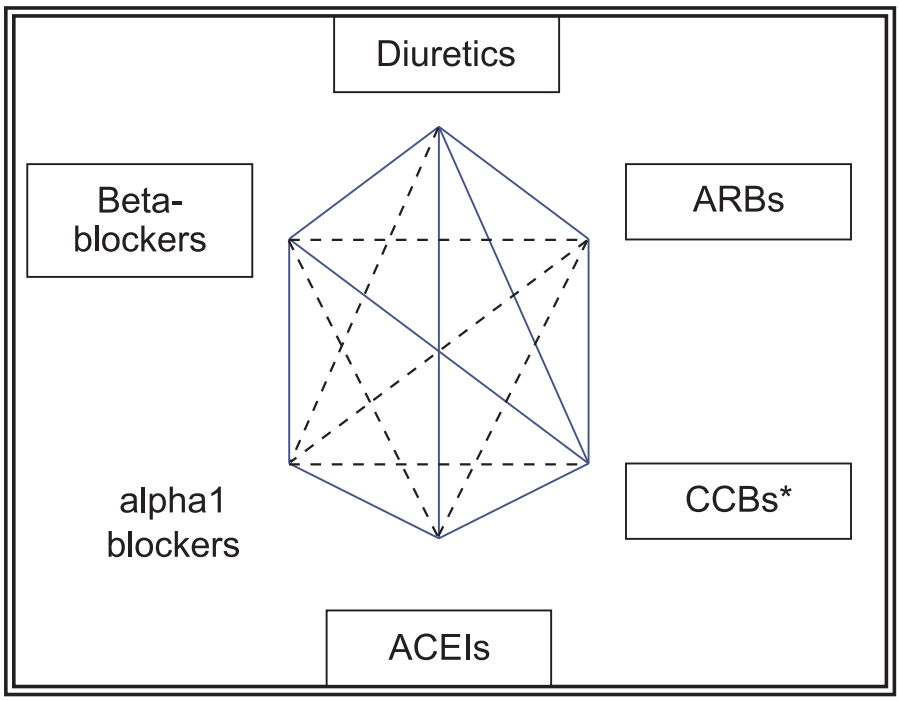

Figure 2. Possible combination of different classes of antihypertensive agents. [11]
The more effective combinations are represented as solid lines. The frames indicate classes of agents shown to be beneficial in controlled interventional studies.
**for concurrent use with beta-blockers, only dihydropyridine group of CCBs should be used.*
ACEIs = angiotensin converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; CCBs = calcium channel blockers

VI PHARMACISTS' ROLE

Hypertension is one of the major chronic diseases where treatment may be associated with non-compliance.[43] Various studies demonstrated that pharmacists' intervention produced significant improvement in BP control in patients with documented hypertension.[44, 45]

To achieve quality pharmaceutical care, we should provide patients with comprehensive counseling: reinforce and educate patients on lifestyle measures, discuss treatment goal with individual patient, encourage self-BP monitoring, help to resolve resistant hypertension (Table 6) especially if it is drug-related, and monitor treatment outcomes and patient compliance. Moreover, a team approach is essential. Pharmacists are in the best position to recommend physicians on the appropriate pharmacotherapies to improve efficacy and safety; provide drug information to other health professionals, and participate in public health campaigns to promote primary prevention of hypertension.

VII CONCLUSION

Hypertension is a life-long problem. The control of BP to treatment goals is

of primary importance in reducing the occurrence of various fatal and non-fatal hypertension-related complications. Maintenance of healthy lifestyle and use of appropriate pharmacological treatments are both important measures.

When deciding on drug therapy, clinical guidelines only serve as a reference for treatment. Since most clinical studies last for only a few years while many complications of hypertension can occur a decade or more later, treatment should therefore be based on individual needs with consideration of underlying diseases and possible drug-drug and drug-disease interactions. Last but not least, managing hypertension through a multidisciplinary approach that integrate the expertise of different health professionals can help to improve patients' concordance which is critical in determining the success of the whole therapy.

Table 6. Causes of resistant hypertension [10]

▲ Undiscovered secondary hypertension (Table 2)
▲ Non-compliance to drug therapy
▲ Failure to undertake lifestyle modification (overweight; heavy drinkers)
▲ Fluid overload (high sodium intake; inadequate diuretic therapy; progressive renal impairment)
▲ Inappropriate measurement of BP (white-coat hypertension; use of unsuitable cuff)

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Genetic Engineering and Large-scale Production of Recombinant Human Erythropoietin

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The large-scale production of erythropoietin (EPO) has been successfully achieved through utilization of "innovative biotechnology" such as structural analysis of carbohydrates, recombinant DNA techniques and cell culture methods. EPO is now clinically available as a biopharmaceutical to treat chronic renal anaemia and other types of anaemia associated with various diseases. It is expected that some more branded products or analogues of EPO with specific physiological effects will soon be developed using the molecular docking technique.

I INTRODUCTION

Erythropoietin (EPO) is a glycoprotein produced in humans by cells of the peritubular capillary endothelium of the renal cortex in the kidney which becomes the primary site of their synthesis shortly after birth[5]. In premature as well as full term infants, the liver, however, is the primary site of EPO production. Synthesis of EPO has also been found in the brain and the uterus, albeit in lesser amounts[9,17]. Some studies suggest that there is an additional contribution from macrophages in the bone marrow[5].

Roles of erythropoietin in blood cell development

EPO is a hormone involved in the regulation of red blood cell production during steady-state conditions and in the acceleration of recovery of red blood cell mass following hemorrhaging[5,6,11,12]. Red blood cells carry oxygen to all tissues in the body while EPO, which is a haemopoietic growth factor, is essential for the final stages of their cell development. In healthy individuals, EPO is produced on a constant rate in kidney but its production is stimulated by the reduction of oxygen in the renal arteries. If oxygen level in the renal arterial circulation decreases, the kidney can detect it and can be stimulated to increase the production of EPO in order to boost the production of red blood cells. On the contrary, when the oxygen level gets too high, production of EPO by the kidneys reduces thereby reducing red blood cell production[5,12,,15].

The principle function of EPO is to act in concert with other growth factors to stimulate the proliferation and maturation of bone marrow erythroid precursor cells (Figure 1)[10]. On the surfaces of burst forming unit-erythroid (BFU-E) cells which are the precursor cells of erythroid, there are many EPO receptors. Circulating EPO binds to these receptors resulting in replication and maturation to functional erythrocytes. *In vitro* studies suggest that EPO may also play a role in thrombocytopoiesis by either synergizing with thrombopoietin to stimulate the proliferation of colony forming unit-erythroid (CFU-E) or inducing both megakaryocyte DNA synthesis and cytoplasmic process formation[1,2]. The growth and differentiation of BFU-Es into CFU-Es requires the presence not only of EPO but also of interleukin-3 (IL-3) and/or granulocyte-macrophage-colony stimulating factor (GM-CSF).

II STRUCTURAL INFORMATION ON THE ERYTHROPOIETIN GENE AND GENE PRODUCTS

Restriction fragment analysis of human lymphocyte DNA using human EPO cDNA as a probe demonstrated the presence of a single band after restriction enzyme digestion. The size of the hybridized bands is similar to that of the originally isolated EPO genomic clone, and hybridization at lower stringency did not show any additional bands. These results indicated that there is only a single copy of the human EPO gene and there are no other genes closely related to the EPO gene or pseudogene. Figure 2 is the restriction map and the schematic diagram of the mRNA transcript of the human EPO gene. Several transcriptional initiation sites have been mapped to nucleotides 105, 118, 123, 135, 141 and 151, and the polyadenylation site has been located at nucleotides 3341-2. The human EPO gene has about 2800 bp and comprises 5 exons and 4 introns which are transcribed and spliced to form a 1200 bp mRNA. The mRNA codes for a protein of 193 amino acids, of which the first 27 amino acids

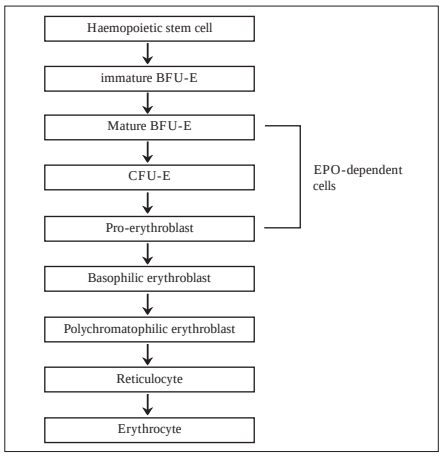

Figure 1. Involvement of EPO in the development of muture of mature red blood cells from haemopoietic stem cells.

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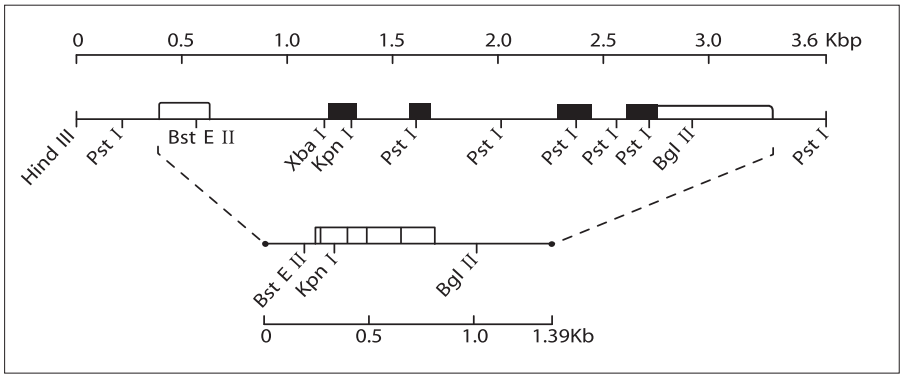

Figure 2. Restriction map of human EPO gene. Exons are indicated by boxes and the solid areas indicate the approximate position of the coding protein of the gene.

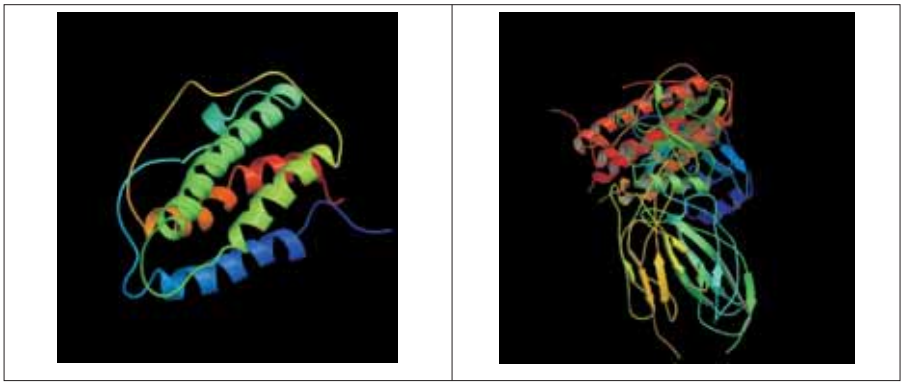

Figure 3. 3-D ribbon structure of human erythropoietin. Left: structure of purified EPO alone; Right: structure of EPO-receptor complex [10].

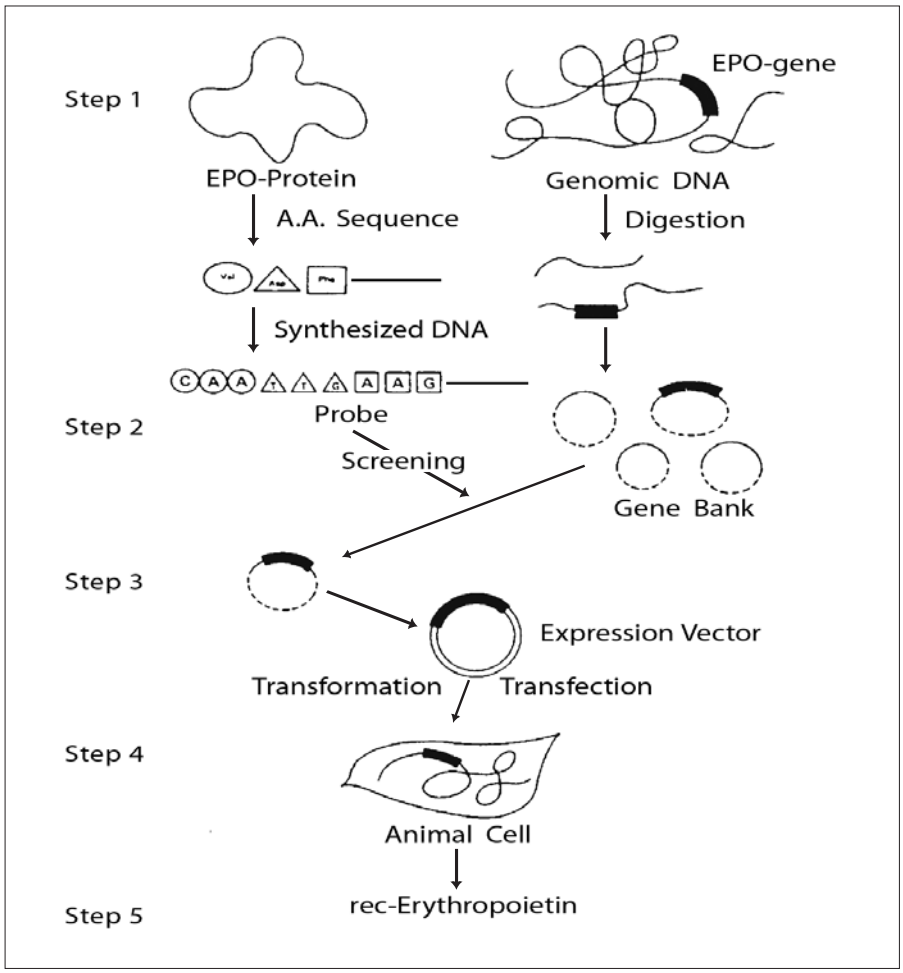

Figure 4. Schematic procedure from EPO gene cloning to expression

are predominantly hydrophobic which is consistent with a signal sequence. The mature protein of 166 amino acids was predicted from the nucleotide sequence. Gene analysis using a hybridoma with chromosome translocated human cells revealed that the EPO gene is located at q11-q22 of the long arm of chromosome 7. To determine homology with the human EPO gene, counterpart genes from monkey and mouse were cloned using the human EPO gene.

Although the cDNA for EPO predicts a molecule with 166 amino acid residues, the mature form of human EPO is a 165 amino acid glycoprotein with a molecular weight of about 36 kDa (Figure 3)[10,13]. This is because a carboxyl-terminal arginine is removed by post-translational modification. In human EPO, the carbohydrate component makes up approximately 40% of its total mass. These sugar moieties were thought to be important for the biological activity of EPO[16]. It has been reported that the binding activity of EPO to acceptor was affected by the degree of glycosylation[3]. There are three potential sites for N-linked glycosylation which apparently is required for full *in vivo* activity. Besides the N-linked carbohydrate, there is also one O-linked carbohydrate moiety attached to the molecule[7,14]. Recent studies indicate that only N-linked, and not O-linked sugars, are important in the functioning of EPO.

III GENETIC ENGINEERING OF RECOMBINANT HUMAN ERYTHROPOIETIN (rHuEPO)

EPO is present in serum and at very low concentrations in urine, particularly of anaemic individuals. Although it has been known for over 100 years, it was not until 1971 that EPO was purified from the plasma of anaemic sheep and small quantities of human EPO were later purified (1977) from over 2500 litres of urine of anaemic patients by Miyake *et al*[4].

The first recombinant human erythropoietin (rHuEPO) was produced in 1983, and within just five years, it was licensed as a therapeutic agent.

i) Cloning of EPO gene

This method was first developed by Lin *et al*. and Jacobs *et al*. in 1985[4,8]. Two peptides, which had relatively low codon degeneracy, were selected from internal tryptic digested fragments. Two mixed oligonucleotide pools, corresponding to these amino acid sequences, were then synthesized and used as non-overlapping probes. One probe mixture contained 20-nucleotide-long oligonucleotides containing all possible coding sequences for an

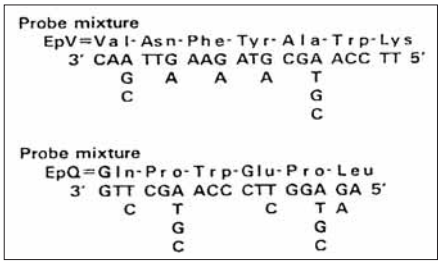

Figure 5. Oligonucleotide probes derived from the EPO peptide fragment. The mixed oligonucleotide pools were synthesized corresponding to the amino acid sequence of a hexapeptide and a heptapeptide derived from internal tryptic digested fragments of EPO. Each probe mixture contained a pool of 128 oligonucleotides.

internal heptapeptide (EpQ); the second mixture contained 17-nucleotide-long oligonucleotides directed against the coding sequence for a hexapeptide (EqV).

The human EPO gene was cloned independently. The process from EPO gene cloning to expression is summarized in Figure 4.

1) Oligonucleotide pools corresponding to the amino acid sequence of EPO tryptic fragments were synthesized. The synthesized oligonucleotides actually consisted of 128 possible combinations.
2) The EPO gene was screened from a human fetal liver genomic library using the synthesized oligonucleotides as cloning probes (Figure 5). Two sets of radiolabeled nucleotide probes were used for sequential hybridization with the EPO gene already inserted in Charon 4A phage. Clones which hybridized with both probes were selected to eliminate false position clones.
3) Expression vector was constructed with the full-length of the identified EPO gene inserted.
4) EPO expression vector was transfected to Chinese Hamster Ovary (CHO) cells.
5) Southern blot analysis revealed that some clones coded for the full-strength EPO gene. The working cell for EPO production was selected from these EPO expressing CHO cells.

There are two approaches to verifying the EPO coding clones identified by sequential hybridization with the oligonucleotide probes. One of them is the comparison of the amino acid sequence predicted from the clone and the partial amino acid sequence of urinary EPO. The other is based on the immunological and biological EPO activity of a glycoprotein expressed in mammalian cells. Human EPO gene clones have subsequently been determined using a genomic gene library of human fetal liver. To determine the cDNA of monkey EPO, an oligonucleotide mixture of human EPO was used to screen the cDNA library constructed from an anaemic monkey kidney induced by phenylhydrazine treatment.

ii) Construction of expression vector of recombinant EPO

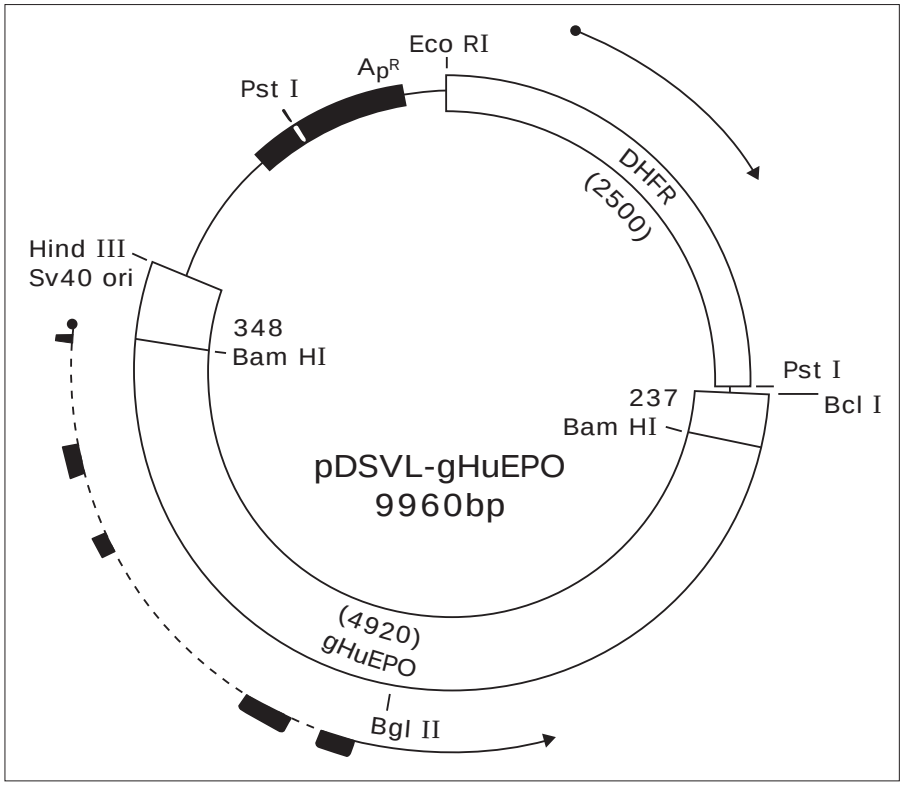

Figure 6. EPO expression vector. The expression vector contained nucleotide fragments of a DHFR mini-gene, a replication origin and promoter derived from simian virus 40 (SV40), and a human genomic EPO gene. Arrows indicate the orientation of transcription.

Since glycosylation is essential for the biological activity of EPO, animal cells were used as host, in most cases, for the production of recombinant EPO. The construction of a high-expression vector and selection of host cell line are also very important for lager-scale production of EPO. As shown in Figure 6, the expression vector contains:

1. a SV40-derived late promoter as a EPO gene expression promoter, the enhancer sequence and the origin of replication
2. a SV40-derived late polyadenylation sequence as a terminator
3. the mouse-derived late dihydrofolate reductase (DHFR) mini-gene for gene amplification
4. pBR322 plasmid-derived replication origin and ampicillin-resistant genes so that replication is possible in selective medium.
5. a BamHI restriction site for insertion of the EPO gene.

The DHFR mini-gene is important in the expression of the rHuEPO gene because it codes an essential enzyme for the *de novo* synthesis of nucleic acids. Methotrexate (MTX), an analogue of folic acid which inhibits dihydrofolate reductase when present in the medium, amplifies the DHFR gene and the EPO gene simultaneously in cells. Since these two genes are connected, cells containing the amplified EPO gene can produce a large amount of EPO in a culture medium. A mutant cell line was used as the host cell to make it easier to select cells containing the amplified DHFR-gene. This mutant cell is a sub-line of the Chinese hamster ovary cell, CHO-K1, which was isolated as a DHFR deficient strain by the tritium suicide method after exposing CHO-K1 Cells to gamma-rays. EPO-producing transformants were actually obtained using the above method in which the EPO expression vector was introduced into the host cell using the calcium phosphate method. These transformants were cultured in the presence of MTX, whose concentration was increased in a stepwise manner to amplify DHFR genes connected to the EPO gene. These EPO-producing candidate cells were obtained for the preparation of master working cells, which are used in the production plant and which secrete the highest amount of EPO in a culture medium. Cells with high productivity were selected using this method and were repeatedly cloned. The master cells were then prepared as production seeds from such cells. The master working cells were stored in polycarbonate tubes in liquid nitrogen and each tube was used to initiate the production of EPO.

iii) Characteristics of rHuEPO

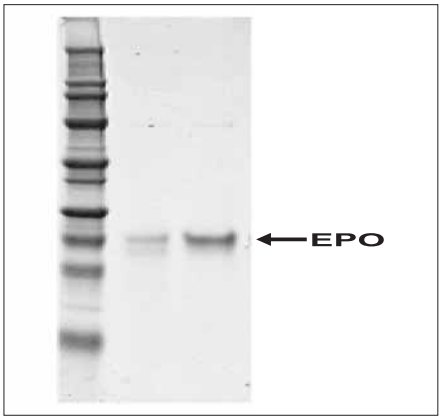

Figure 7. SDS-PAGE gel of HPLC purified recombinant erythropoietin. Left lane is molecular weight marker.

Although mature EPO expressed by baby hamster kidney (BHK) cells contains 166 amino acids, the molecular weight of rHuEPO may be slightly different depending on the host system. The molecular weight of rHuEPO varies from 38 to 42 kDa on SDS-PAGE and 28 kDa by HPLC (Figure 7). Nevertheless, it was confirmed that all recombinant molecules of EPO contain 4 cysteine residues and that there are 2 disulfide bonds between positions 29 and 33 and between position 7 and 161. Similar findings regarding the post-translational processing of amino acids at the carboxyl terminal conformed to EPO purified from human urine. Analysis of Circular dichroism spectra revealed that the protein moiety of rHuEPO contains an alpha-helix as a secondary structure and that the ratio of the alpha-helix moiety is about 50%.

In the rHuEPO molecule, there are 3 Asn-X-Ser/Thr sequences where N-glycosylation takes place. Asn-linked sugar chains are found attached to these sites at positions 24, 38 and 83. A mucin-type sugar chain also attaches to the serine residue at position 126.

These findings are in good accordance with those of human urinary EPO. Isoelectric focusing also showed similar profiles for human urinary EPO and rHuEPO, with isoelectric points (pI) of 3.5-4.5. The specific biological activity of recombinant EPO determined using hypoxic hypervolemic mice should not less than $1.5x10^5$ IU/mg. Very similar dose-response curves of human urinary EPO and recombinant EPO using this method indicate that the two types of EPO have similar biological characteristics.

IV CLINICAL APPLICATIONS OF rHuEPO

There are some diseases with which anemia is frequently associated in addition to renal failure, rheumatoid arthritis, various types of cancer, AIDS, infections as well as bone narrow transplantation. This kind of symptom is due to the loss or the drop in number of red blood cells. Thus, the therapeutical uses of rHuEPO accelerate or stimulate erythropoiesis and clinical applications can be divided into three categories:

- Replacement therapy - treatment of patients who are unable to produce sufficient levels of EPO in the body
- Rescue therapy - overcoming the inhibitory effects on the body's supply of EPO caused by naturally occurring factors in the body or drugs
- Enhancement therapy - enhancing the normal process of erythropoiesis

Human recombinant EPO is widely used throughout the world to treat anaemic patients with chronic renal failure, cancer and HIV infection. Some studies had shown the benefit of rHuEPO for anaemia associated with chronic renal failure. Besides, rHuEPO had been used in surgery and oncology. There are many other reports indicating new applications to anaemia in prematurity, multiple myeloma and aplastic anemia. At the beginning of its clinical development, it was assumed that rHuEPO might not be so effective when given by subcutaneous administration because the rHuEPO molecule is a highly glycosylated protein with high molecular weight, and only intravenous administration was expected to be suitable for clinical application. However, clinical efficacy by subcutaneous administration was better than predicted and this form of administration can lead to much longer retention of rHuEPO in the blood than same dose intravenous administration. A new high-concentration formulation for subcutaneous injection has been developed and this has made it possible to reduce the frequency of administration and to expand the clinical applications. Many clinical applications of rHuEPO are still under trial for various forms of anaemia, such as anaemia associated with cancer treatment and anaemia accompanying BMT.

Table 1. Recombinant Erythropoietin Products currently available in the world

Product	Main Ingredient	Manufacturer
Eprex®	Recombinant Human EPO Alpha	Janssen
Epogen®	Recombinant Human EPO Alpha	Amgen
Procrit®	Recombinant Human EPO Alpha	Ortho Biotech
Neorecormon®	Recombinant Human EPO Alpha	Boëhringer-Mannheim
Dynepo®	Recombinant Human EPO Alpha	Aventis
Epomax®	Recombinant Human EPO Alpha	Baxter
Replagal®	Recombinant Human EPO Alpha	Transkaryotic Therapies
Recormon®	Recombinant Erythropoietin Beta	Roche
Darbpoetin alfa®	Recombinant Human EPO Alpha, 2nd generation	Amgen
Aranesp®	Recombinant EPO analogue	Amgen
Nespo®	Recombinant EPO analogue	Dompé Biotec

V CONCLUSION

By far the most common use of rHuEPO is for the treatment of anaemia caused by chronic kidney failure (renal anaemia). It is generally given as an injection under the skin. In this aspect, rHuEPO is used as a replacement therapy. Numerous studies have proven rHuEPO to be extremely effective, not only in correcting renal anaemia, but also in reducing the risk of cardiac complications and improving patients' quality of life. The only real alternative to rHuEPO treatment in renal anaemia is replacement of the missing red blood cells with regular blood transfusions. While this is less expensive than rHuEPO treatment, it does have a number of drawbacks, not least of which is the risk of blood-borne infection from contaminated blood products. In addition, the supply of rHuEPO is effectively limitless, while the supply of blood for transfusion is limited to the availability of donated blood. Marketing survey indicated that by the end of 2001 the world market for rHuEPO was valued at US$5.3 billion, a growth of 12% over 2000. The market has been growing at an 11% average annual growth rate over the previous 5 years. Based on quarterly sales figures from participating companies, the market in 2002 was around US$5.9 billion, again a 12% growth over 2001. It seems that demand of this therapeutic agent is growing steadily. After more than a decade of study and exploration, there are already a bunch of recombinant products of erythropoietin available in the world (Table 1). It is expected that some more branded products based on existing techniques or technique based on molecular docking for more specific curing purposes are in the pipe line as patents for EPO production are going to expire.

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Antiemetic, Antiatherogenic and Nonsteroidal Antiinflammatory Effects of Ginger (薑/姜)

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Botanical Name: *Zingiber officinale* (薑, Common ginger); *Curcuma longa* (薑黃,Turmeric ginger,)
Plant Family: *Zingiberaceae*
Other Names: Gengibre, Gingembre, Zenzero, Cochin Ginger, Shengjian(生薑), Shoukyo, Kankyo (干薑)
Brand Names: Bioactive Ginger®, Gingersel®, Bio-Organics Arthri-Eze Forte®, Extralife Arti-Care®, Frontier Ginger®, Ginger Powder, Ginger Extract,.

I ABSTRACT

Ginger or Zingiber is the rhizome of *Zingiber officinale*. It has been used for centuries as a culinary spice, to reduce flatulence, bloating, indigestion and to stimulate the appetite. It is used by Chinese for illnesses thought to be caused by cold and dampness. The dried extract of ginger contains monoterpenes and sesquiterpenes. The main bioactive principles in ginger are the gingerols and shogoals and some related phenolic ketone derivatives. Recent studies indicate that ginger has the potential to be of clinical use to stop nausea, to treat inflammatory conditions of the musculoskeletal system and may have some beneficial effects in the cardiovascular system. Ginger is one of the most popular nutraceuticals throughout history.

II DESCRIPTION AND BACKGROUND

Ginger (Figure 1) is the dried rhizome of *Zingiber officinale* Roscoe (Figure 2, left photo). It is a perennial plant belonging to the family *Zingiberaceae* that consists of another 47 genera such as *Curcuma, Alpinia* (Figure 2, right photo), *Amomum, Elettaria, Hedychium, Phaeomeria etc*. It is a native plant to Southeast Asia[7] but it has been planted throughout Africa, Eastern Europe and the West Indies by Europeans before the seventeenth century. The ginger plant is propagated by rhizome cuttings which are planted in Spring.The current leading producers are Indonesian, Chinese and Jamaican, while the leading consumers are Arabian, American, Japanese and European.

Fresh ginger appears in irregular piece. It is slightly compressed with finger-like branches of about 4 - 18 cm long and 1 - 3 cm thick. Externally, it is yellowish or greyish-brown and ringed. The top of each branch exhibits a steam scar or buds. Texture of the herb is fragile and easily broken. Freshly broken surface looks pale yellow with well-marked endodermis rings and scattered vascular bundles. It has a strong aromatic odour and is characterized by a pungent taste. The rhizome bears buds on the top of each of its stubby fingers, and grows a mass of thin, tangled roots below. The ginger plant is about 1 to 3 m high and sturdy with a solid stem covered in alternate linear leaves[11]. It is monoecious and

Figure 1. Fresh rhizome of Zingiber officinale

Contraindications
Not to be taken during pregnancy and lactation. Because ginger increases bile flow, people with gallstones should only use it after consultation with a physician.

Undesirable Effects
Fresh ginger is quite safe with appropriate use. Dried root may cause mild heartburn if used excessively. Otherwise, no undesirable effect has been reported

Interaction with Conventional drugs
Caution is required whenever taken with anticoagulant (e.g., warfarin, heparin) or antiplatelet (e.g., aspirin) drugs at an excessive dietary intake of ginger may potentiate their effects.

Figure 2. Flower of Zingiber officinale (left) and Alpinia purpurata (right).

produces an orchid like flower with petals that are greenish-yellow streaked with purple[2,43].

Ginger was known to the Chinese nearly 2,500 years ago[41]. Most gingers are used as spice or flavor due to its pleasant aroma but also for drug purposes. It was used by the Greeks and Romans as a spice[4,42] whereas the Africans and the West Indians used it as a medicine. The buds of some gingers such as myoga (*Z. mioga*) in Japan and torch ginger (*Phaeomeria elatior*) in Malaysia and Thailand, and the leaves and young stems of some other gingers are edible. Dietary supplement preparations of ginger mainly use the rhizome, which is the most valuable part of *Z. officinale*.

Ginger is a common ingredient in more than half of the prescriptions of Traditional Chinese Medicines (TCM)[4]. In TCM, the fresh rhizome of *Z. officinale* is called "shoukyo" while the dried rhizome is called "kankyo" and their applications are quite different from each other. The Chinese utilized dried ginger for aches, asthma, bleeding, cholera, diarrhea, heart conditions, nausea, respiratory disorders, rheumatic complaints, stomach ache and toothache[2,4,24,43]. However, fresh ginger is used as an antiemetic, carminative, digestive stimulant and diuretic[41]. The medical use of Ginger was first documented by Marco Polo in the late 13th century[42].

III BIOACTIVE CONSTITUENTS

Ginger contains a diverse range of biologically active compounds[11]. A comprehensive description of the constituents of ginger can be found in a chapter written by Kikuzaki[17]. The true value of ginger is basically found in two groups of special compounds; namely the essential oil found in the tiny vessels just under the flaky skin and the oleoresin which is located in specialized cells dotted around the fleshy interior of the rhizome. The latter type of compounds can only be extracted and concentrated by using alcohol or organic solvents.

The primary pungent component in the rhizome of *Z. officinale* is a gingerdiol derivative, named gingerol (薑辣素), followed by two aromatic ketones, zingerone (薑酮) and shogoal, which are gingerol-ralated compound. As Figure 3 shows, gingerol is a noncyclic decane having a 4-hydroxyl-3-methoxyphenyl group at C-1, a carbonyl group at C-3 and a hydroxyl group at C-5. Chief compounds of gingerdiol include: [6]-gingerol, [8]-gingerol, and [10]-gingerol, depending on the length of the alkyl chain. Fresh rhizomes of ginger cultivated in Southeast Asia contain approximately 0.3-0.5% [6]-gingerol and 5-20% of the other two types of compound. Many studies have shown that gingerols and shogals are the bioactive principles in ginger responsible for its' beneficial effects in the body.

The shogoal group of compounds, including [6]-shogaol, [8]-shogaol, [10]-shogaol, is another component group also responsible for the pungency of ginger, albeit having smaller effect. It structurally belongs to monodehydrated gingerol.

Besides the gingerdiols and shogoals, ginger contains many diarylheptanoids such as gingerenone

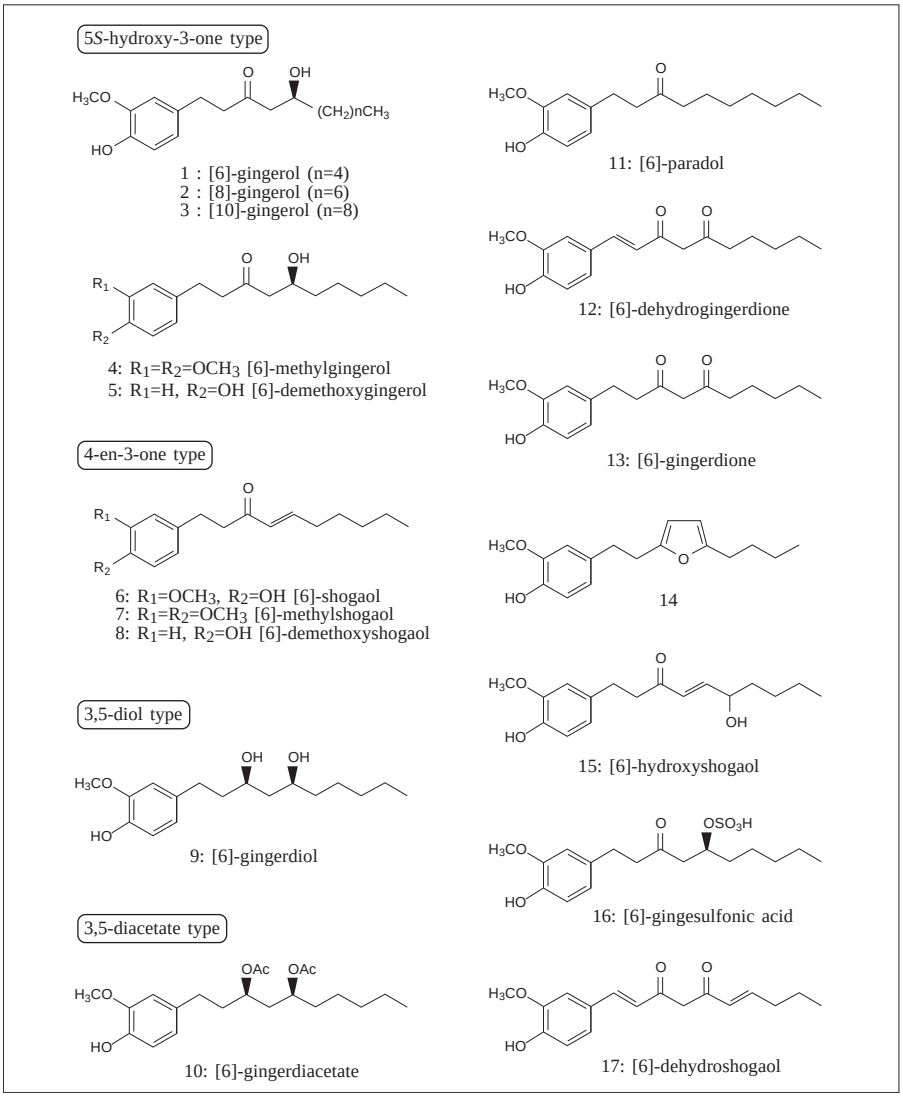

Figure 3. Gingerol-related compounds isolated from the Rhizome of Zingiber officinale[17].

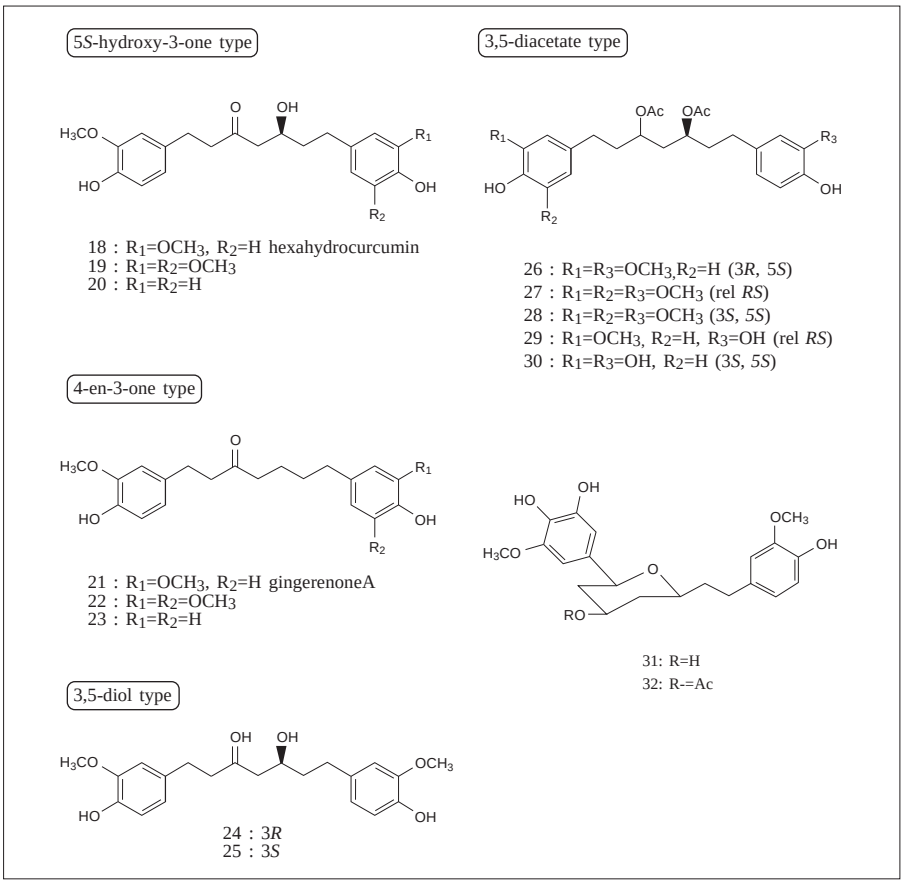

Figure 4. Diarylheptanoids isolated from the rhizome of Zingiber officinale[17].

A and B (Figure 4); terpenoids such as geraniol, geranylacetate and geranial and volatile oil. Their quantities can vary greatly depending upon country of origin. The volatile oil contains sesquiterpenes such as zingiberene, arcurcumene, beta-bisabolene and ar-curcumene, neral and geranial, D-camphor, beta-phellandrene, geranial, neral, linalool and (E)-alpha-farnesene, important as the aroma carrier of zingiberol (a mixture of cis- and trans beta-eudesmol). In general, ginger contains more than 50 per cent of starch.

IV CONTEMPORARY USES

Although ginger is commonly used as a flavor and condiment in food, it is also a remedy. Table 1 summarizes some substances in ginger which have biological effects on human health. Its warming, circulating and relaxing properties make it applicable to a wide range of conditions. Contemporary herbalists recommend ginger for colds and flu. The Chinese use ginger's papery brown skin to treat people with wind and gas, the peeled root to treat nausea, dysentery and to act as an overall digestive stimulant. In Trinidad the root is used for indigestion. In Brazil it is used to treat cramps, nausea and gas. Western herbalists use ginger as a stimulating carminative.

Ginger is effective for motion sickness, seasickness and morning sickness especially during pregnancy[5,8]. As it has a high content of antioxidants, it is a free radical scavenger. Thus, it has been considered as an antimutagenic and anti-inflammatory nutraceutical[18,19,23].

In the Pharmacopoeia of the People's Republic of China, fresh ginger is indicated to induce perspiration and dispel cold. It can warm the stomach and arrest vomiting. It can resolve phlegm and relieve cough.

Recent clinical studies have proven it effective in improving appetite, a medicine for digestion problems[32], prevention of postoperative nausea and vomiting[3,31] and the treatment of arthritis and cardiovascular problems.

V MODE OF ACTION

1. Antiemetic and antinauseant effects

Nausea and vomiting may occur as a side-effect of drugs, poisons, anaesthetics or toxins in the body. The antiemetic effects of ginger extracts have been extensively explored[6,9,14,31,35,36]. A double-blind randomized clinical trial reported in 1995 to investigate the effect of ginger on nausea and vomiting following gynaecological laparoscopic surgery was conducted by Arfeen *et al*[1]. It was reported that both 0.5 and 1.0 g ginger were effective in reducing nausea, with only the higher dose being effective at reducing vomiting. At St. Bartholomew's Hospital, 60 patients were given ginger against post-operative nausea and vomiting, which are side-effects of the anaesthetics. It was found that those taking ginger had much less nausea and vomiting than the others. None of the women taking ginger needed any anti-vomitting drugs after the operation, in contrast to those in the other groups[6]. A similar conclusion was reached in another study that conducted that ginger was as effective as metoclopramide in reducing postorperative nausea and vomiting[31]. In both studies treatment with ginger reduced the need for other antiemetics during the postoperative period. Cisplatin induced emesis but

Table 1. Biological effects of substances from ginger

Substance	*Biological effects*
Asparagine	Promotes urination
Borneol	Analgesic, anti-inflammatory, lowers fever, liver protective
Chavicol	Kills fungi
Cineole	Anaesthetic, clears chest/throat infections and cough, antiseptic, lowers blood pressure
Citral	Antihistamine, antibiotic
Cymene	Anti-flu, kills viruses and fungi
Dehydrogingerdione	Inhibits prostaglandins, treats liver
Geraniol	Anti-candida
Gingerdione	Inhibit prostaglandins
Gingerols	Analgesic, lowers fevers, stimulates circulation, lowers blood pressure, treats and calms stomach
Hexahydrocurcumin	Treats liver, stimulates bile
Linalool	Prevents convulsions, antiseptic
Myrcene	Kill bacteria, relaxes muscles
Neral	Kill bacteria
Pinenes	Removes phlegm
Shogaol	Analgesic, lowers fevers, sedative, constricts blood vessels, raises blood pressure

not emesis due to apomorphine, was effectively prevented by giving mongrel dogs the acetone and ethanolic, but not aqueous, extract of ginger[36]. These results suggest that the prophylactic antiemetic substances of ginger are present only in the ethanolic or acetone fraction and possibly involve different mechanisms.

When Mowrey and Clayson prescribed some capsules containing 940 mg of dried ginger powder to persons who suffered from motion sickness, they observed an improved response to motion in the patients. The improvement was even better than dimenhydrinate, an antihistamine available over-the-counter for the problem of motion sickness[29]. Ginger juice produces anti-motion sickness action possibly by central and peripheral anticholinergic and antihistaminic effects. A study conducted by Qian and Liu discovered that the improvement in response to motion sickness was attributed to the release of substance P from sensory fibres in the ileum after exposure to the pungent constituents in ginger. The released substance, in turn, either stimulated cholinergic and histaminic neurons to release acetylcholine and histamine, respectively, or produced direct muscle contraction by activating M and HI receptors, correspondingly. It was proposed that after being excited by the substance P, M and HI receptors were inactive temporarily and unable to be excited by agonists, therefore, ginger juice exhibited anticholinergic and antihistaminic actions[33].

2. Anti-atherosclerosis effects

Coronary artery disease develops as a result of various risk factors, including increased plasma LDL levels, as well as LDL modifications, such as oxidation or aggregation. Consumption of phenolic flavonoids in the diet has been shown to be inversely associated with morbidity and mortality from coronary heart disease[12,13, 21,30]. Ginger contains a lot of phenolic compounds and has been found to prevent heart-attack or stroke by significantly reducing the level of LDL cholesterol and the oxidative state of LDL in plasma[10,34]. Figure 5 shows that both oxidation and aggregation power of LDL were significantly inhibited by regular consumption of ginger extract. As Figure 6 shows, the anitoxidation capacity of ginger in comparison to vitamin E is actually much stronger. Activity of antithromboxane synthetase that correlates with its ability to inhibit aggregation of human platelets in response to ADP, collagen, and epinephrine was correlated to the dose of aqueous extract of ginger given. Figure 7 is a photomicrograph revealing that development of atherosclerosis could be attenuated by regular consumption of a high dose of ginger[10,38]. In the placebo group, lesions were large and consisted of many lipid-laden macrophage foam cells (Fig. 7A) while after consuming 250 μg of ginger extract per day, the lesions were significantly smaller and contained only a few foam cells in mice (Fig. 7B).

When rats were regularly fed with ginger, the activity of hepatic cholesterol-7α-hydroxylase, the rate-limiting enzyme in bile acids biosynthesis, was enhanced and the conversion of cholesterol to bile acids was stimulated. Consequently, it eliminated cholesterol from the body[37]. It was concluded that consumption of ginger extract may be proven beneficial in attenuation of atherosclerosis development, since it is associated with reduced macrophage-mediated oxidation of LDL, reduced uptake of oxidized LDL by macrophages, reduced oxidative state of LDL and reduced LDL aggregation. All these effects lead to a reduced cellular cholesterol accumulation and foam cell formation, the hallmark of early atherosclerosis. Thus, it has benefical effect on the cardiovascular system.

3. Nonsteroidal anti-inflammatory effects

Ginger has been used as an anti-inflammatory substance and marketed as products for the treatment of arthritis for long time. The medical application of ginger in this aspect, however, was first investigated in depth just two decade ago [25,40]. However, more than 100 papers have been published in the last few years about the anti-inflammatory and antitumor promoting effects relevant to ginger with the objective of elucidating the molecular mechanism of their effect.

Srivastava and Mustafa reported that more than 75% of patients receiving 3-7 g powered ginger daily for 56 days had a significant reduction in pain and swelling associated with either rheumatoid- or osteo-arthritis. No adverse effects were reported from this chronic use of relatively high doses of ginger[39]. It has been confirmed that the anti-inflammatory effects are a result of inhibition of prostaglandin release, and hence ginger acts like a nonsteroidal anti-inflammatory drug which basically interferes with the release or biosynthesis of prostaglandin[20,25,39]. Jana *et al* reported that ginger was as

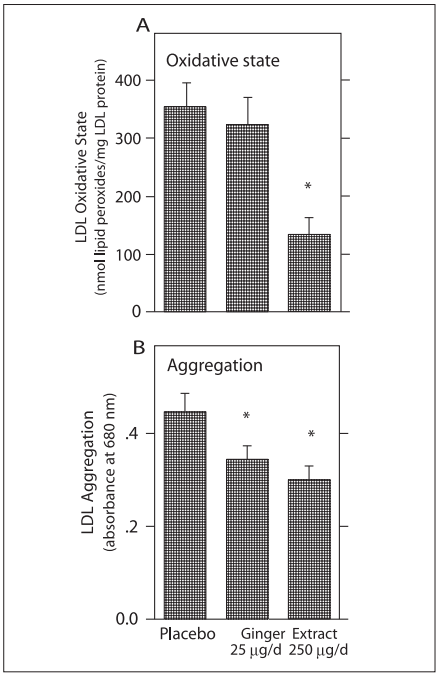

Figure 5. Effect of ginger consumption on oxidation (A) and aggregation (B) of LDL in apolipoprotein E-deficient mice[10].

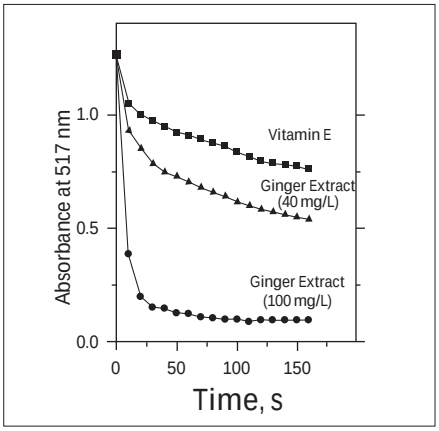

Figure 6. Free radical scavenging capacity of ginger extract[10].

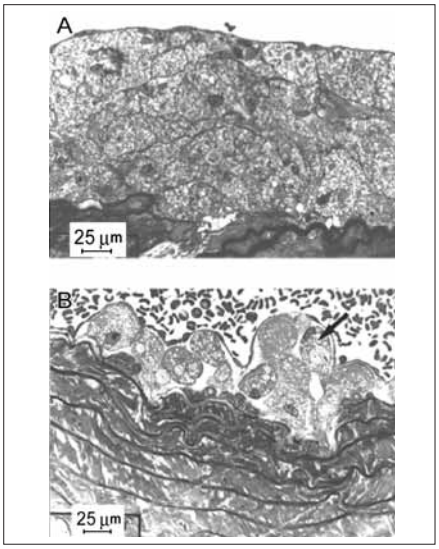

Figure 7. Atherosclerotic lesion of the aortic arch of apolipoprotein-deficient mice after treatment with placebo (A) or with ginger extract (dose: 250 ug/d)(B)[10]. The arrows indicate location of foam cells.

effective as aspirin, in reducing carrageenin induced oedema in rats[16].

4. Other actions

Huang *et al* reported that [6]-dehydrogingerdione, [8]- and [I0]-gingerol were anticathartic[15]. They found that serotonin (5-HT) induced hypothermia could be inhibited after ingestion of an acetone extract of ginger at a dose of 100 mg/kg. The active component responsible for this effect was [6]-gingerol and shogaol.

Ginger is a pungent bitter herb which increases both gastric motility and secretion. It has the ability to increase digestive fluids, plus absorb and neutralize toxins and stomach acid. Bile secretion, as well as the action and tone of the bowels were increased in the presence of ginger.

VI CONTRADICATIONS[1,6,27,44]

Pregnancy and lactation. People taking anticoagulant and antiplatelet drugs. People with gallstones. Patients with "sensitive" stomachs may not always tolerate ginger.

VII UNDESIRABLE EFFECTS

At the moment of this publication, no undesirable effect has been reported.

VIII INTERACTIONS WITH CONVENTIONAL DRUGS[28,40,43]

Ginger may decrease the therapeutic effect of antacids due to increased secretion of gastric after taken the herb. The therapeutic effect of cholesterol lowering drugs even thought via different mechanism may be enhanced. The vasodilating properties of ginger on gut wall may increase drug adsorption. Ginger also affects bleeding time and should not be taken by patients using warfarin.

XI MODE OF ADMINISTRATION

Ginger is commercially available as capsules, dried powered root, syrup, tincture, tablets, tea, oral solution, powder for oral solution, and in candy, beer and ice-cream[7].

X DOSAGE

Unless otherwise stated on the manufacturer's label, recommended daily dosages are:

- ▲ Fresh ginger root: *1/4*- to *1/2*-inch (peeled) slice up to three times a day.
- ▲ Standardized extract in pill form: 100 to 200 mg up to three times a day.
- ▲ Fresh powdered ginger: *1/2* to *3/4* teaspoon up to three times a day.

The total daily dose of ginger is 2 to 4 g. The antiemetic dose is 2 g of the freshly powered rhizome taken with some liquid[11].

XI DURATION OF APPLICATION

No specified duration of application period has been found among different countries.

XII REGULATORY STATUS

Germany: Commission E approves ginger for dyspeptic complaints and the prevention of motion sickness[7].
United Kingdom: Registered as an over-the-counter (OTC) drug.
United States: Dietary Supplement.
AHPA Botanical Safety Rating: Class 1[26].

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香港醫院藥劑學會2003年會長報告

Ng, Kim Wah

今年是繁忙的一年，三月「沙士」的來臨，令整個香港陷於健康、經濟危機，香港整體也面臨重大的考驗。政府政策與民意背向，更令港人飽受政治上的動盪與不安，社會穩定亦處於崩潰的邊緣。

儘管如此，我們成功地創辦了藥物教育資源中心及償還自置會址的所有債務，在此亦呼籲各會員參與和使用會所的設施。我衷心感謝學會全體委員及藥物教育資源中心，盡心盡力、竭盡所能的為本會服務，各項活動已表列於 Table 1 中。 特別要感謝的是藥物教育資源中心的兩位項目總監，由其是崔俊明先生在「沙士」肆虐期間作出的貢獻，大家是有目共睹。因此，今年的「會長年獎 (President's Award)」將會授予崔先生，以表揚他對藥劑界的貢獻。

「一波才動萬波隨」，希望大家亦爭相參與對藥劑業的推動，希望逆境即將過去！我們在檢討過去工作的不足之餘，亦需要計劃將來，在來年的計劃裏，仍需大家付出努力，才能令藥劑業的目標如願以償。更希望大家能暫忍逆境帶來的痛苦，包容我工作不善不足之處，相信我們全體委員已全力以赴，並期盼來年更上一層樓。為達致更理想的目標，希望能爭取到大家的認同和參與推動來年以下的項目：

一. 培養年青新一代的藥劑師加入委員會，參與會務及推動藥劑專業的工作。

二. 與政府衛生署繼續商談兩個項目：
   (甲) 正式成立藥劑業管理委員會 (Pharmacy Council)
   (乙) 醫院藥劑師在「藥劑及毒藥委員會」(Pharmacy and Poisons Board) 的代表問題。

三. 成立「藥物教育資源基金」，目標不少於一百萬港元。

以上三個目標是極之難辦到的，是個夢想又是個挑戰。夢想在我來說好比登月的難，盼望是大家同心同德，努力前往 ；好像我國首位航天員上太空一樣，在太空中轉數十圈並不是甚麼一件史無前例的創舉，但在意義上卻標誌著歷史的新一頁---中國踏進科技興國的開端。明年SHP的目標能否成功、能否達標我不敢說，但我總覺得信心乃建立在盼望、相信、忍耐和大家的進取上，讓我們攜手為香港醫院藥劑的專業，建立一個良好的基石。 時光更變如走馬，最後送給大家一首【李賀〇夢天】的詩，願大家抓緊時光，共創前程 --- 老兔寒蟾泣天色，雲樓半開壁斜白。玉輪軋露濕團光，鸞珮相逢桂香陌。黃塵清水三山下，更變千年如走馬，遙望齊洲九點煙，一泓海水杯中瀉。

Table 1. SHP & DERC Activities and Events in 2003

Date	Activities / Events (A total of 47 activities or events)
15/12/2003	Attended the Advisors Meeting Seminar by LEGCO Member Michael Mak. Speaker Dr PY Lam on Structure of CDCHK
11/12/2003	Speech on the Function of DERC & SHPHK at a Forum with Shanghai Pharmacists organized by Roche
6/12/2003	Attended the 40th Anniversary of Chinese University of Hong Kong
4/12/2003	Interview by SCMP "招職" on Job situation of pharmacist in HK
3/12/2003	Meeting with Chairman & committee member of Braincare Hong Kong
2/12/2003	Joint Press Release with "Hong Kong Men's Health" on Survey of Impotency
29/11/2003	Appointed as the committee member of editorial board of 衛生部中國藥房雜誌
21/11/2003	Participated in Hong Kong Pharmacy Consortium as a member
15/11/2003	與PPA聯署向衛生處反映「不良醫藥廣告」新加附表事宜
14/11/2003	Forum with DERC Sponsors
10/11/2003	Discussion meeting with Presidents of PS & PPA on current Pharmacy issues (Joint HKPJ, HK Pharmacy Conference & Joint PCCC)
11/10/2003	DERC與 PPA在香港藥劑週年專業會議發表「公私營藥物輔導計劃」
8/11/2003	Lecture given to CUHK Intern Pharmacists
7/11/2003	Meeting with DERC Advisors and Volunteer Pharmacists
8/10/2003	會見衛生處討論「不良醫藥廣告」新加附表事宜
17/9/2003	會見衛生福利局局長反映業界問題
16/9/2003	香港電一台 精靈一點—專題訪問會長 公私營合作「藥物輔導計劃」
16/9/2003	Participate in National Day Banquet & Ceremony
5/9/2003	Hong Kong Pharmacy Consortium Group Meeting
14/08/2003	Meeting with the SARS Expert Committee Hong Kong
26/06/2003	First Shphk GC meeting at the DERC
19/06/2003	DERC Training Program of Clinic Nurse Graduation Ceremony
01/06/2003	【醫藥人】醫藥龍門陣會長每月專欄文章及專題訪問會長

Date	Activities / Events (A total of 47 activities or events)
05/05/2003	出席浸會大學中藥學學會成立就職典禮
02/05/2003	經濟日報健康版「維他命」專題訪問會長
2/05/2003	香港電一台 精靈一點 專題訪問會長 「防炎用藥」
01/05/2003	【醫藥人】「防炎熱線」特稿
28/04/2003	SHPHK新聞稿「停止不理性的謾罵」
28/04/2003	主持DERC-Watsons 「防炎熱線」開幕典禮
26/04/2003	拍攝「防炎熱線」宣傳影片
23/04/2003	RTHK查小欣、張堅庭 「維他命」專題訪問會長
17/04/2003	TVB program series interview the DERC Education Program Director Mr. William Chui on SARS related issues
17/04/2003	Joint Press Statement on Taking High Dose Vitamins
14/04/2003	Re-launching of SHPHK Website
14/04/2003	Reconstruction of SHPHK Member's communication tree
12/04/2003	DERC Renovation commenced
10/04/2003	DERC 藥劑師提供抗炎資訊 (明報醫療網)
06/04/2003	Delivered a Joint Statement to Public on use of SARS treatment drugs (Ribavirin)
05/04/2003	「藥劑師抗炎大聯盟」印製及提供全港藥房向市民派發「防炎問藥單章」
04/04/2003	Organized Train the trainer workshop on SARS for pharmacists' public talk
31/03/2003	Organized SARS Forum for Community Pharmacists
11/03/2003	Press Release on Survey revealing response of patients on the New Drug Charge Policy
27/02/2003	Meeting with Consumer Council HK for joint Education Projects
26/01/2003	DERC Inauguration Ceremony & SHPHK AGM
18/01/2003	Talked to Macau Hospital Pharmacists on Public Pharmacy Education
14/01/2003	Attended HKAPI Annual Dinner
06/01/2003	Participated in Hong Kong Pharmacy Conference as committee members

Note: A detail list of the educational programmes and activities organized by the Drug Education Resource Centre during the period of July 2002 to December 2003 are available upon request from the HKPJ editorial committee (e-mail: pharmjhk@yahoo.com).

The Practicing Pharmacists Association of Hong Kong - *President Interim Report*

Chung, Billy

It has been quite a memorable and eventful year 2003 for Hong Kong. The most frightening and unforgettable experience encountered by most of us was the SARS outbreak that had taken many valuable lives away including the healthcare professionals. This was a very good lesson to learn in how to appreciate our loved ones, a healthy living environment, to take care of our family members, friends, colleagues, patients and especially the under privileged in the society as a primary healthcare provider.

It was definitely quite a memorable and eventful year of 2003 for the PPA also. As the President of the PPA since last May, I am very privilege to represent my new GC team to present this interim report to you all.

To facilitate the smooth, efficient and effective running of activities within the PPA, our team has successfully set up a set of GC Guidelines to complement the present M&A. The GC guidelines laid down clear, proper and sensible standards for all GC members to follow and I am very happy to report that the internal and external PPA affairs had been fruitfully conducted under this rational, fair and transparent system.

The Pharmacy Practice Standard and Development subcommittee has unreservedly articulated the PPA stands on several issues regarding the situation of pharmacy continuing education down the road, how medical devices; health claims of health products and the labelling of nutritional repackaging should be regulated.

The Continuous Improvement Workshop subcommittee has successfully organized a couple of hands-on workshops on medical devices and wound dressings. A Pharmacist Training Program will later be introduced to help develop our patient counselling skills, personal selling techniques and the managerial skills on minor ailments.

In reaching out to our members electronically, PPA is proud to have a brand new website design that most information could be circulated instantly to all members by the eNews. This channel of communication has also created a platform for members to immediately voice out their concerns relating to any issues by logging on our web forum.

PPA has also prepared for the foreseeable change in the community practice by setting up a standard prescription labelling system on-line. PPA has organized a number of computer courses for our members to prepare for this electronic new era. Computers will be used to print dispensing labels when filling prescriptions.

The bi-monthly newsletter, our traditional channel of communication, guarantees to keep members, with or without computers, abreast of the latest development of the Association. Our newsletter team worked diligently and has effectively produced some masterpieces in covering some current events in the pharmacy practice, the Association activities and the latest development in the "Public-Private Partnership Program" (4P).

PPA has actively worked together with other pharmaceutical organizations to demonstrate the professionalism of pharmacy profession to the general public. PPA has taken part in the decisions making of the Pharmacy Central Continuing Education Council (PCCC) and the Hong Kong Pharmacy Consortium. For the very first time in PPA history, PPA has become one of the organisers of the October 2004 Pharmacy Conference. PPA has formed an alliance with the Drug Education Resources Centre (DERC), a task force of the Society of Hospital Pharmacists of Hong Kong (SHPHK). This alliance provides some golden opportunities for our members to jointly give counsellings to different patients' groups with our hospital partners. PPA has also worked with the Pharmaceutical Society of Hong Kong (PSHK) in the drafting of the Standard Operational Procedures (SOP) for the community practice.

PPA is a member of the 4P advisory committee as well as the working group, which are headed by the Chief Pharmacist and the Senior Pharmacist of Hospital Authority (HA) respectively. PPA has strongly instilled the importance of the 4P to members and the Authorised Seller of Poisons (ASP). Through the 4P, community pharmacists have the opportunity to provide counselling services and to monitor drug compliance (DCCS) of the patients referred by the HA hospitals. In order to ensure a better service to the patients, community pharmacists are expected to attend two training courses organized by the PCCC in April and May. An on-site training at the designated hospitals in June completes the full course of training. The DCCS program will then be officially launched in July 2004.

It is so very inspiring to see PPA achieve so much in just the past few months. I am extremely pleased to have such a capable, dedicated and competent GC team to work synergistically together for the benefits of our members and the profession. PPA appreciates the importance of cooperation and by joining all our efforts; we should definitely see the "Ray of Hope" in our profession.

Date of Report: March 10th 2004

2003 Statistics from the Pharmacy Central Continuing Education Committee (PCCC)

Continuing Education Units (CEU) obtained	*Number of PCCC members**
12 or above**	180
1 - 11	706

**The total number of PCCC members was 886 in 2003.*
***Members who obtained more than 12 CEUs in 2003 are entitled to Certificates from PCCC.*
The CEUs required was specially adjusted for 2003 from 20 to 12 because of the SARS outbreak.

PSHK President Report 2003 - *Apocalypse of SARS*

Kwong, Benjamin

Nature calls again. This time it came hard and full of challenge and misery. It seems that we all have forgotten that hidden danger is always around us. Are we too complacent about our present environment and achievement and we are too lax in complying the basic requirement? SARS has reflected totally how bad we are in the area of personal hygiene and public health. Lesson has been learnt and I sincerely hope that we do not need to foot another bill for another painful lesson.

SARS has triggered me to think again about life from a different prospective. Not only on personal but also its implications on our Pharmaceutical Society of Hong Kong (PSHK)? Could it give us some insights to our future direction? Let me share with you what I see SARS stands for in the PSHK. Select Activity to Reach Standard. This is what PSHK has been doing for and thank to the most energetic and enthusiastic team of the General Council members, we have done a lot despite the interruption by the SARS period.

1. Communication Standard

Each PSHK member is provided an e-mail account for communication. Over 95% of our members can be reached by this mean and information can be disseminated more efficiently and timely.

PSHK website is continuously developing and more and more features are added to it. A member corner is established and our Pharmaspect newsletter will be posted up for easy access and save a few trees from an environmental point of view.

2. Pharmaceutical Care Standard in Old-Aged home

PSHK continues the Chi Lin Nunnery project and has set the standard of the pharmaceutical service which an old-aged home should have. We are promulgating this concept to other institutions and hopefully when the economy recovers fully, more and more homes will implement it.

3. Practice Standard

PSHK has initiated the drawing up of a dispensing standard with the joint effort from all other pharmacist organizations. This is an on-going project and our aim is to have one standard set by our own profession in Hong Kong.

4. Continuing Education Standard

PSHK has devoted to the joint effort in setting the standard on professional continuing education with other pharmacist organizations. The Hong Kong Pharmaceutical Journal, The Hong Kong Pharmacy Conference and The Pharmacy Central Continuing Education Committee are all setting the scene and are contributing to the setting up of the standard.

Apart from these activities, our Pharmacy & Poisons Board members are working hard to push for standard in local pharmacist training, drug classifications and the finale is our regulations standard. We all agree that our Ordinance and Regulations are not up to a modern society standard. Due to the present political environment, a total revamp of the legislations is almost impossible. PSHK and the Board members' representatives would select the most appropriate area to set the relevant standard first.

Our annual publication "OTC at a Glance" is receiving its recognition and status. It will carry on developing and meeting the needs identified.

Finally, on behalf of the 2003 General Council, I would like to thank you for your support and contribution to PSHK and continue being a PSHK member. Rest is assured that our membership drive will strive for the better.

SARS reminds us the importance of the basic and the danger of being high-sounding only. PSHK will work on the basic to strengthen the foundation for future development of the pharmacy profession. Surely I must not forget the basic which I must express my heartfelt thanks to this year General Council members. Without their support and hard work I will have nothing to write in this report.

Peter Leung, Ken Hau, John Lau, Grace Lau, Vivian Ma, Winnie Ng, Shadow Lee, Candy Tai, Cindy Ho, Peter Chua, Chi Kit Chan, Henry Lau, Warren Tsang, Chi Ming Wong

Yours truly,
Benjamin Kwong

Pharmaceutical Society of Hong Kong 2004 General Council Members

President:	Mr.Benjamin Kwong
Vice-President:	Mr. Peter Leung
Honorary Treasurer:	Mr. John Lau
Honourary Secretary:	Ms. Ritchie Kwok

Other GC Members:

Mr. Chan Chi Kit	Dr. Grace Lau
Mr. Henry Lau	Mr. Warren Tsang
Mr. Ken Hau	Mr. Perry Sit
Mr. Philip Chiu	Mr. Rico Yau
Ms. Shadow Lee	Ms. Winnie Ng
Mr. Wong Chi Ming	

Society of Hospital Pharmacists of Hong Kong General Committee Members 2004

President:	Mr Kim Wah Ng
Vice President:	Mr So Yiu Wah
Secretary:	Mr Patrick Lee
Treasurer:	Mr Law Kwok Ming

Other GC Members:

Ms S. C. Chiang	Mr Chow Hiu Fung
Mr Frank Chung	Ms Wanda Kwan
Mr Humphrey Lam	Dr Benjamin Lee
Mr Robin Li	Mr Michael Ling
Mr Charles Lo	Mr Freddie Poon
Mr Eric Wong	

Pharmacy Exhibition - *Feb 20-21, 2004*

The Pharmacy Exhibition, jointly organized by the Chinese University of Hong Kong, Pharmacy Society, Lion Club of Metropolitan Hong Kong and the Chinese University of Hong Kong, School of Pharmacy, was held on Feb 20-21 at Metroplaza, Kwai Fong. That event focused on educating the general public for the correct use of medications.

Dr Ko Wing Man of Hospital Authority, Dr T.H. Leung of Department of Health, Mr Edwin Tam of Loins Club and Professor Moses Chow of School of Pharmacy officiated the event at the opening ceremony on February 20. Moreover, Mr Samuel Chan Kin Fung was invited as the Pharmacy Health Ambassador.

Apart from normal exhibitions, brochures were freely distributed and several registered pharmacists were physically presented to give advices to public.

A more detailed report regarding the Pharmacy Exhibition authored by the Chinese University of Hong Kong, Pharmacy Society shall be published in the next HKPJ issue.

The Public Private Partnership Program (4P) for Pharmacy Service - *the First Ever Collaboration Project in the History of Pharmacy Service*

Chiang, S C, Senior Pharmacist, Chief Pharmacist's Office;
Lam, Wency, Pharmacist, Chief Pharmacist's Office

I INTRODUCTION

To better meet the health care needs for the population in Hong Kong, the Hospital Authority (HA) undertakes, as one of its business initiatives in the 2003/04 Annual Plan, to enhance the public private interface in the provision of care. Under this initiative, HA has set several business targets to collaborate with the private sectors; amongst these include the setting up of mechanisms and means to facilitate the transfer of information, skills and knowledge from the public to the private sectors so that some of the provision of care for the patients can appropriately take place at the primary care or community care settings.

For the pharmaceutical service, it has been emphasized that pharmacy staff in HA should work in partnership with other health care professionals to support the direction on the development of ambulatory and community care programmes and to replace, where appropriate, in-patient treatment by ambulatory and out-patient services.

II THE ADVISORY COMMITTEE

Basing on the above development direction, the Chief Pharmacist's Office (CPO) and the frontline pharmacies of HA has reached a conclusion to devise appropriate Public - Private Partnership Programmes for the pharmacy service by collaborating with the professional societies, so that our patients can be referred to the community pharmacies for the management of their medications and medication related problems. To follow up on the issue, an Advisory Committee on Public Private Partnership Programme (4P) for Pharmacy Service has been formed. This Advisory Committee, chaired by the Chief Pharmacist of HA, has membership, comprising of representatives from HA, the Pharmaceutical Society of Hong Kong (PSHK), the Practicing Pharmacists Association of Hong Kong (PPA) and the Society of Hospital Pharmacists of Hong Kong (SHPHK).

III THE WORKING GROUP ON PATIENTS REFERRAL SCHEME ON DRUG COMPLIANCE AND COUNSELLING SERVICE

As medication compliance is a common problem for our patients and due to the large patient volume in the public sector, it is considered as a matter of priority for the Public Private Partnership Programme to focus first in this area so that immediate attention and assistance can be provided to the concerned group of patients in order to improve their understanding on their drug therapy and thus improving their drug compliance. For this purpose, the Working Group on Patients Referral Scheme on Drug Compliance and Counselling Service (DCCS) is set up and will be responsible to come up with the appropriate action plans in order that patients from the public can be referred referred to the private community sectors about their medication problems through established protocols and approved mechanisms.

IV THE RECRUITMENT CRITERIA FOR COMMUNITY PHARMACISTS INTO DCCS

To ensure the success of the Public Private Partnership Programme and the Patients Referral Scheme on DCCS, it is necessary that uniform and optimum standards are set on the provision of pharmaceutical practice at the community pharmacies. This is also to protect the interests of patients, hospital pharmacists and community pharmacists participating in the DCCS. For these reasons, Community Pharmacists wishing to participate in the DCCS must fulfill the recruitment criteria which comprise of the following areas:-

A. Professional Qualification & Requirement

A.1 Possess a valid license to practice as a registered pharmacist in Hong Kong;
A.2 Currently working full time in a Community Pharmacy;
A.3 Possess a minimum of 1-year of post-graduate experience in local or overseas hospital or community setting of pharmacy practice;
A.4 Fulfill the accreditation and training requirement as endorsed by the Working Group and organized by Pharmacy Central Continuing Education Committee (PCCC).

B. The Community Pharmacy Practice Site

B.1 There should be an acoustically/ visually private area available in the Community Pharmacy for the Pharmacists to conduct the patient counselling and review the patients' medication;
B.2 There should be readily available information resources such as current edition of reference textbooks (e.g. BNF, HKIMS, drug interaction handbook, Martindale) or electronic means such as computer to access drug information via e.g. the internet;

B.3 Community Pharmacists must display conspicuously his /her own registration certificate and the annual practicing certificate in the Community Pharmacy;
B.4 Community Pharmacists must be able to distinguished himself / herself to the patients from other personnel working in the Pharmacy by wearing his/her name card and observing a professional dress code;
B.5 Community Pharmacists should inform the Working Group on the DCCS of any change of workplace 1 month in advance of such change.

C. *Professional Ethics & Legal Requirement*

C.1 Community Pharmacists should respect the patients' right to maintain their data privacy and confidentiality at all times during counselling sessions and in the documentation and storage of patient records, with reference to the Personal Privacy Data Ordinance requirement;
C.2 Community Pharmacists should offer a "free-of-charge" service on the Patients Referral Scheme on DCCS;
C.3 Community Pharmacists should avoid making use of the counselling sessions for promotion of sales of products unrelated to DCCS to the patients;
C.4 Community Pharmacists should not accept any unused or expired medications from the patients and should advise the patients that these should be returned to the hospital pharmacy at their next follow up visits.

Table 1. DCCS - Training Schedule

Module I: Professional knowledge development

Topic	Date	Time	Venue	Speaker
Asthma	14 April 2004	6:30 - 9:30pm	HA Building	Dr. C.K. Ng Medical Officer (Respiratory Specialist), Department of Medicine, Queen Elizabeth Hospital Mr. Robin Li Pharmacist North District Hospital
Hypertension	19 April 2004		Ruttonjee Hospital	Dr. Bernard Cheung Associate Professor, Department of Medicine, HKU
Diabetes Mellitus	26 April 2004		Ruttonjee Hospital	Dr. Juliana Chan Associate Professor Department of Medicine and Therapeutics, CUHK Dr. Wilson Leung Pharmacist Queen Elizabeth Hospital
Workshop (4 identical sessions available)	24 April 2004	9am - 11am, 11am - 1pm, 2pm - 4pm 4pm - 6pm	HA Building	Dr. May Fok Assistant Professor, School of Nursing, The Hong Kong Polytechnic University

Module II: Personal skills

Topic	Date	Time	Venue	Speaker
Interpersonal communication skills	20 May 2004	6:30 - 9:00pm	HA Building	Mr. Chester Tsang Human Resources Manager (Training & Professional Development) Hospital Authority

Module III: Practical training on DCCS

Starting date: Beginning of June
Length of session: 3 - 4 half day sessions
(To be arranged by Partnership Hospital Pharmacist of the Community Pharmacist)

Section	Topic
1	HA Pharmacy Operations
2	Orientation of local hospital
3	Attending the Compliance Clinic with the Hospital Pharmacist
4	Optional Specialty Training

V THE PARTICIPATING CRITERIA FOR HOSPITAL PHARMACISTS INTO DCCS

For the participating hospital pharmacy in HA, the Hospital Pharmacists should also meet the following criteria:

- Minimum of 1 year experience working in the hospital system in HA
- Fulfilled the annual Continuous Professional Development (CPD) requirement by Chief Pharmacist's Office in HA
- Attended the appropriate training programmes on communication and counselling skills
- Possessed the knowledge on how to retrieve the information from the Clinical Management System (CMS), ePatient Records (ePR), Corporate Drug Dispensing History (CDDH)
- Have experience in the operation of the Medication Compliance Clinic, Warfarin Clinic, or similar service

VI ENROLMENT REQUIREMENT

The Patients Referral Scheme on DCCS is not automatically opened for all or any Hospital/Community Pharmacists. Community Pharmacists, wishing to participate, need to follow the enrolment procedures and these are subjected to an evaluation and approval process laid down by the Advisory Committee on the Public Private Partnership Programme on Pharmacy Service.

VII TRAINING AND ACCREDITATION REQUIREMENT

To ensure the standard of the Patients Referral Scheme on DCCS, it is necessary to set some basic accreditation and training mechanism to enable the qualifying Community Pharmacists to successfully assume his/her full role in the DCCS. To commence the program, the Community Pharmacists should firstly participate in the training modules. The Working Group, through the PCCC, would have endorsed a set of specially designed training programmes/workshops. The training programmes/workshops will cover the latest development of drug treatment guidelines on specific disease groups and aim to enhance the pharmacists' knowledge in disease management. Also, the training programme/workshops will cover personal development skills to improve the performance of the community pharmacists in drug counseling. Please see table 1 for details on the training schedule.

VII CONCLUSION

As the Patients Referral Scheme on DCCS is a collaboration project newly introduced to our Hospital Pharmacists and Community Pharmacists, its success requires the professional support rendered by both parties. It is expected that through the development and implementation of this program, a service network between Hospital and Community Pharmacists can be established; and that trust and respect from our patients for our Community Pharmacists can be enhanced and that many medication-related problems for our patients could be minimized or prevented through the long-term monitoring of drug compliance and through patient counseling by our community pharmacists and ultimately our patients will be empowered to make their choice of pharmacists' support from the community sector in their medication management in the long run.

P/S. For details about the program, all inquiries should be directed to : The Program Executive Secretary at Chief Pharmacist's Office, 10/F., Block A, PYNEH, 3, Lok Man Road, Chaiwan, Hong Kong.

NEW PRODUCTS

LEVITRA
(Bayer and GlaxoSmithKline)

Active ingredient:
Vardenafil hydrochloride trihydrate

Presentation:
Available in 5mg, 10mg and 20mg film-coated tablet

Pharmacological Properties:
Vardenafil is a potent and selective inhibitor of the cGMP specific phosphodiesterase type 5 (PDE5), the most prominent PDE in the human corpus cavernosum. Vardenafil potently enhances the effect of endogenous nitric oxide in the corpus cavernosum by inhibiting PDE5. When nitric oxide is release in response to sexual stimulation, inhibition of PDE5 by vardenafil results in increased corpus cavernosum levels of cGMP. Sexual stimulation is therefore required for vardenafil to produce its beneficial therapeutic effects.

Indications:
Treatment of erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for LEVITRA to be effective, sexual stimulation is required.

Dosage & Administration:
Adult men - 10mg once per day taken as needed approximately 25 to 60 minutes before sexual activity. Based on efficacy and tolerability the dose may be increased to a maximum of 20mg or decreased to 5mg. LEVITRA can be taken with or without food. The onset of activity may be delayed if taken with a high fat meal.

Elderly men - Since vardenafil clearance is reduced in elderly patients, a first dose of 5mg should be used. Based on efficacy and tolerability the dose may be increased to 10mg and 20mg.

Contraindication:

Hypersensitivity; the coadministration of vardenafil with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated; agents for the treatment of erectile dysfunction should generally not be used in men for whom sexual activity is inadvisable (e.g. patient with severe cardiovascular disorders); concomitant use of vardenafil with potent CYP3A4 inhibitors (ritonavir, indinavir, ketoconazole and oral form of itraconazole) is contraindicated in men older than 75 years; women

Precautions:
Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Use with caution in patients with anatomical deformation of the penis, or in patients who have conditions which may predispose them to priapism. The safety and efficacy of combinations of vardenafil with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended. Concomitant intake of grapefruit juice is expected to increase the plasma concentrations of vardenafil. The combination should be avoided.

Drug Interactions:
Co-administration of the HIV protease inhibitor indinavir (800mg tid), a potent CYP3A4 inhibitor, with vardenafil (10mg) resulted in a 16-fold increase in vardenafil AUC and a 7-fold increase in vardenafil C_{max}.

Co-administration of ketoconazole (200mg), a potent CYP3A4 inhibitor, with vardenafil (5mg) resulted in a 10-fold increase in vardenafil AUC and a 4-fold increase in vardenafil C_{max}.

Co-administration of erythromycin (500mg tid), a CYP3A4 inhibitor, with vardenafil (5mg) resulted in a 4-

fold increase in vardenafil AUC and a 3-fold increase in C_{max}. When used in combination with erythromycin, vardenafil dose adjustment might be necessary.

Grapefruit juice being a weak inhibitor of CYP3A4 gut wall metabolism, may give rise to modest increases in plasma levels of vardenafil.

Side effects:
Digestive: dyspepsia, nausea
Nervous System: dizziness
Cardiovascular: flushing
Respiratory: rhinitis
Body as a Whole: headache

Forensic classifications:
P1S1S3

VFEND (Pfizer)

Active Ingredient:
Voriconazole

Presentation:
Each vial contains 200 mg voriconazole equivalent to a 10 mg/ml solution following reconstitution
Each tablet contains 50 mg or 200 mg voriconazole

Pharmacological Properties:
In vitro, voriconazole is a broad spectrum, triazole antifungal agent, displays antifungal potency against *Candida* species and fungicidal activity against all *Aspergillus* species tested. In addition voriconazole shows *in vitro* fungicidal activity against emerging fungal pathogens, including those such as *Scedosporium* or *Fusarium* which have limited susceptibility to existing antifungal agents. Its mode of action is inhibition of fungal cytochrome P450-mediated 14α-sterol demethylation, an essential step in ergosterol biosynthesis.

Indications:
Treatment of invasive aspergillosis; treatment of fluconazole-resistant serious invasive Candida infections (including C. *krusei*); treatment of serious fungal infections caused by *Scedosporium* spp. & *Fusarium* spp. VFEND should be administered primarily to immunocompromised patients with progressive, possibly life-threatening infections.

Dosage & Administration:
Therapy must be initiated with the specified loading dose regimen of either intravenous or oral VFEND to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of the high oral bioavailability (96%), switching between intravenous and oral administration is appropriate when clinically indicated.

Use in adults and Adolescents (12 to 16 years of age):
Intravenous*
LD - 6 mg/kg q12h; MD - 4 mg/kg bd
Oral - ≥ 40 kg
LD - 400 mg q12h; MD - 200 mg bd
Oral* - < 40 kg
LD - 200 mg q12h; MD - 100 mg bd

Children aged 2 to < 12 years:
Intravenous / Oral
LD - 6 mg/kg q12h; MD - 4 mg/kg bd

** LD = Loading Doses (for first 24 hours); MD = Maintenance Doses (after first 24 hours)*

Contraindications:
Hypersensitivity; Coadministration of terfenadine, astemizole, cisapride, pimozide or quinidine, rifampicin, carbamazepine, Phenobarbital, ergot alkaloids (ergotamine, dihydroergotamine) and sirolimus (see drug interaction below).

Precautions:
Caution should be used in prescribing VFEND to patients with hypersensitivity to other azoles. Infusion-related reactions, predominantly flushing and nausea, have been observed during administration of the intravenous formulation of voriconazole. Acute renal failure has been observed in severely ill patients undergoing treatment with VFEND.

Drug Interactions:
Rifampicin (600 mg once daily) decreased the C_{max} and AUCτ of voriconazole by 93 % and 96 %, respectively.

Although not studied, carbamaze-pine or phenobarbital are likely to significantly decrease plasma voriconazole concentrations.

Coadministration of voriconazole with terfenadine, astemizole, cisapride, pimozide, or quinidine is contraindicated, since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of *torsades de pointes.*

Voriconazole increased sirolimus (2 mg single dose) C_{max} and AUCτ by 556% and 1014%, respectively.

Although not studied, voriconazole may increase the plasma concentrations of ergot alkaloids (ergota-mine and dihydroergotamine) and lead to ergotism.

Coadministration of voriconazole (300 mg twice daily) with warfarin (30 mg single dose) increased maximum prothrombin time by 93 %.

Although not studied, voriconazole may increase the plasma levels of sulphonylureas, (e.g. tolbutamide, glipizide, and glyburide) and therefore cause hypoglycaemia.

Although not studied, voriconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity.

Side effects:
Body as a whole: Fever, headache, abdominal pain
Cardiovascular: Hypotension, thrombophlebitis, phlebitis
Digestive: Nausea, vomiting, diarrhoea
Haemic and lymphatic: Thrombocytopenia, anaemia (including macrocytic, microcytic, normocytic, megaloblastic, aplastic), leukopenia, pancytopenia, purpura
Metabolic and nutritional: Peripheral oedema
Skin and appendages: Mild to moderate severity rash
Visual disturbances: altered/ enhanced visual perception, blurred vision, colour vision change or photophobia. The visual disturbances are transient and fully reversible.
Liver: Voriconazole has been infrequently associated with cases of serious hepatic toxicity in patients with other serious underlying conditions. This includes cases of jaundice, and rare cases of hepatitis and hepatic failure leading to death.

Forensic classification:
P1S1S3

NEW INDICATION

TAMIFUL (Roche)

Active ingredient:
Oseltamivir phosphate

New Indication:
TAMIFUL is indicated for the treatment of influenza in children with 1 year of age or older.

Dosage & administration:
Treatment. Treatment begins within the first or second day of onset of symptoms of influenza and the recommended duration is 5 days. The oral dose in children depends on the body weight of the child:

Body Weight	*Dose*
</=15 kg	30 mg* bd
>15 kg - 23 kg	45 mg* bd
>23 kg - 40 kg	60 mg* bd
> 40 kg	75 mg bd

** Tamiflu 12 mg/ml powder for oral suspension is available.*

ERRATUM

In the New Products Section of HKPJ Issue 4 Vol 12, the manufacturer of LANTUS should read as "Aventis" instead of "Adventis". We express our sincere apology to the company.

NEW

FOR TYPE 2 DIABETES...

When Patients on Metformin Do Not Reach Goal,

DOUBLE TEAM IT

AVANDAMET™ - THE LEADING TZD AND THE LEADING ORAL ANTIDIABETIC (OAD) IN ONE!

WITH THE DURABLE POWER OF TWO

- **DISTINCT ACTION:** Complementary mechanisms that target core defects, resulting in improvements in insulin sensitivity and estimates of beta-cell function[1]
- **DEPENDABLE THERAPY:** Low incidence of hypoglycemia[1]
- **ADDITIONAL CONTROL:** Combination of rosiglitazone and metformin provides additional glycemic control than metformin alone[2]

Further information is available upon request.
Avandia, Avandamet are registered trademarks of the GlaxoSmithKline group of companies.

References: 1. Avandamet (package insert). Research Triangle Park NC: GlaxoSmithKline; October 2002 2. T. A. Jones, M. Sautter, L. F. Van Gaal and N.P. Jones. Addition of rosiglitazone to metformin is most effective in obese, insulin-resistant patients with type 2 diabetes Diabetes, Obesity and Metabolism, 2003; 5 : 163-170

GlaxoSmithKline

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

NEW Avandamet™
rosiglitazone maleate/metformin HCl

DURABLE POWER OF TWO

ABBREVIATED PRESCRIBING INFORMATION Presentation Each Avandamet™ film-coated tablet contains 500mg metformin hydrochloride and 1mg, 2mg or 4mg rosiglitazone as the maleate. **CLINICAL INFORMATION Indications** AVANDAMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are already treated with combination rosiglitazone and metformin or who are not adequately controlled on metformin alone. Management of type 2 diabetes mellitus should include diet control. Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but also in maintaining the efficacy of drug therapy. Prior to initiation or escalation of oral antidiabetic therapy in patients with type 2 diabetes mellitus, secondary causes of poor glycemic control, e.g., infection, should be investigated and treated. The safety and efficacy of AVANDAMET as initial pharmacologic therapy for patients with type 2 diabetes mellitus after a trial of caloric restriction, weight loss, and exercise has not been established. **DOSAGE AND ADMINISTRATION General** The selection of the dose of AVANDAMET should be based on the patient's current doses of rosiglitazone and/or metformin. The safety and efficacy of AVANDAMET as initial therapy for patients with type 2 diabetes mellitus have not been established. The following recommendations regarding the use of AVANDAMET in patients inadequately controlled on rosiglitazone and metformin monotherapies are based on clinical practice experience with rosiglitazone and metformin combination therapy. • The dosage of antidiabetic therapy with AVANDAMET should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of 8 mg/2000 mg. • AVANDAMET should be given in divided doses with meals, with gradual dose escalation. This reduces GI side effects (largely due to metformin) and permits determination of the minimum effective dose for the individual patient. • Sufficient time should be given to assess adequacy of therapeutic response. Fasting plasma glucose (FPG) should be used to determine the therapeutic response to AVANDAMET. After an increase in metformin dosage, dose titration is recommended if patients are not adequately controlled after 1-2 weeks. After an increase in rosiglitazone dosage, dose titration is recommended if patients are not adequately controlled after 8-12 weeks. **Dosage Recommendations For patients inadequately controlled on metformin monotherapy:** the usual starting dose of AVANDAMET is 4 mg rosiglitazone (total daily dose) plus the dose of metformin already being taken (see Table 5). **For patients inadequately controlled on rosiglitazone monotherapy:** the usual starting dose of AVANDAMET is 1000 mg metformin (total daily dose) plus the dose of rosiglitazone already being taken (see Table 5).

Table 5. AVANDAMET Starting Dose

PRIOR THERAPY	Usual AVANDAMET Starting Dose	
Total daily dose	Tablet strength	Number of tablets
Metformin HCl*		
1000 mg/day	2 mg/500 mg	1 tablet b.i.d.
2000 mg/day	1 mg/500 mg	2 tablets b.i.d.
Rosiglitazone		
4 mg/day	2 mg/500 mg	1 tablet b.i.d.
8 mg/day	4 mg/500 mg	1 tablet b.i.d.

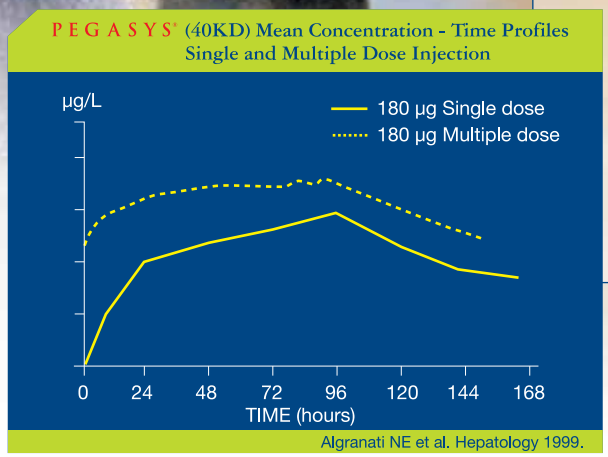
*For patients on doses of metformin HCl between 1000 and 2000 mg/day, initiation of AVANDAMET requires individualization of therapy.

When switching from combination therapy of rosiglitazone plus metformin as separate tablets: the usual starting dose of AVANDAMET is the dose of rosiglitazone and metformin already being taken. **If additional glycemic control is needed:** the daily dose of AVANDAMET may be increased by increments of 4 mg rosiglitazone and/or 500 mg metformin, up to the maximum recommended total daily dose of 8 mg/2000 mg. No studies have been performed specifically examining the safety and efficacy of AVANDAMET in patients previously treated with other oral hypoglycemic agents and switched to AVANDAMET. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur. **Specific Patient Populations** AVANDAMET is not recommended for use in pregnancy or for use in pediatric patients. The initial and maintenance dosing of AVANDAMET should be conservative in patients with advanced age, due to the potential for decreased renal function in this population, Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of AVANDAMET. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly (see WARNINGS). Therapy with AVANDAMET should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy) (see PRECAUTIONS, Hepatic effects and CLINICAL PHARMACOLOGY, Hepatic Impairment). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with AVANDAMET and periodically thereafter (see PRECAUTIONS, Hepatic effects). **Contraindications** Rosiglitazone maleate and metformin hydrochloride tablets are contraindicated in patients with:- Renal disease or renal dysfunction - Congestive heart failure requiring pharmacological treatment - Known hypersensitivity to rosiglitazone maleate and metformin hydrochloride - Acute or chronic metabolic acidosis, including diabetic ketoacidosis **Warnings and Precautions • Type I diabetes mellitus** Rosiglitazone-metformin is effective only in the presence of insulin and should not be used in type 1 diabetes mellitus. **• Premenopausal anovulatory women** Rosiglitazone-metformin treatment in premenopausal anovulatory patients with insulin resistance may result in resumption of ovulation. These patients may be at risk of pregnancy. **• Lactic Acidosis** Lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation. Associated risk factors of lactic acidosis, should be assessed prior to initiation of metformin, and therefore rosiglitazone-metformin, therapy. If lactic acidosis is suspected, rosiglitazone-metformin should be discontinued and the patient should be hospitalised immediately. **• Renal impairment** Serum creatinine levels should be determined before initiating treatment with rosiglitazone-metformin and regularly thereafter. Special caution should be exercised in patients likely to have renal impairment, or in situations where renal function may become impaired. **• Hepatic impairment** Rosiglitazone-metformin is not recommended in patients with hepatic impairment. **• Cardiovascular** Thiazolidinediones can cause fluid retention, which can exacerbate congestive heart failure. The fluid retention may very rarely present as rapid and excessive weight gain. Patients at risk for heart failure (particularly those on insulin) should be monitored for signs and symptoms of heart failure. Rosiglitazone-metformin is not recommended in patients with acute or severe cardiac failure unless the potential benefit is believed to outweigh the potential risk. **• Iodinated contrast agent** Rosiglitazone-metformin should be discontinued prior to, or at the time of the test and not reinstituted until renal function has been confirmed as normal. **Interactions ➢ Rosiglitazone** In vitro studies demonstrate that rosiglitazone is predominantly metabolised by CYP 2C8, with CYP 2C9 as only a minor pathway. **➢ Metformin** There is an increased risk of lactic acidosis in acute alcohol. **Pregnancy and Lactation Fertility** Rosiglitazone-metformin treatment in premenopausal anovulatory patients with insulin resistance may result in resumption of ovulation. These patients may be at risk of pregnancy. **Pregnancy** Adequate data are not available for rosiglitazone-metformin during pregnancy in humans. **Lactation** Adequate data are not available for rosiglitazone-metformin during lactation in humans. **Adverse Reactions ➢ Rosiglitazone** Adverse experiences with rosiglitazone were generally not dose related, were mostly mild and transient in nature. In a small number of patients treated with rosiglitazone adverse experiences of oedema (dose-related), anaemia (decreased haemoglobin) and hypercholesterolaemia were reported in double blind studies. In clinical trials, an increased incidence of heart failure has been observed when rosiglitazone is used in combination with insulin compared to insulin alone. Patients who experienced heart failure were on average older, had a longer duration of diabetes, and were mostly on the higher 8 mg daily dose of rosiglitazone. Dose-related weight gain was seen with rosiglitazone alone and in combination with other hypoglycaemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation. Patients receiving rosiglitazone in combination with insulin or oral hypoglycaemic agents may be at risk for hypoglycaemia, and a reduction in the dose of the concomitant agent may be necessary. Post marketing reports of CHF and pulmonary oedema have been received rarely. Post marketing reports of hepatic dysfunction, primarily evidenced by elevated hepatic enzymes have been received rarely, although a causal relationship to rosiglitazone has not been established. **➢ Metformin** Gastrointestinal symptoms nausea, vomiting, diarrhoea, abdominal pain and loss of appetite Metallic taste Mild erythema Lactic acidosis

N03AV50/12-2003

PEGASYS®
peginterferon alfa-2a

Seeking The Best Chance for a Cure in Hepatitis C



Enhanced Pharmacokinetics
~ True 7-day viral suppression with once weekly dosing

Unsurpassed Efficacy
~ Particular in genotype 1 infection and high viral load

Easy Administration
~ Simple fixed dose, ready-to-use solution

PEGASYS® plus ribavirin had an overall sustained viral response in HCV-infected patients of 56%.[1]

For HCV genotype 1 patients with high viral load, the sustained viral response is 41% for combination therapy with PEGASYS® versus 33% with conventional interferon plus ribavirin.[1]

Full prescribing information is available upon request

Reference:
1.Fried MW, Shiffman ML, Reddy KR, et al. Combination of peginterferon alfa-2a plus ribavirin in patients with chronic hepatitis C virus infection. New Engl J Med 2002; 347 (13):975-982

Roche

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