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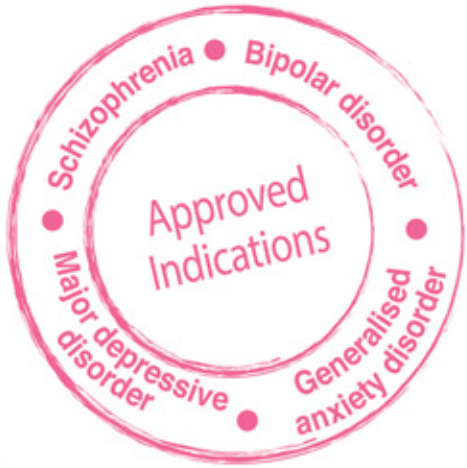
Seroquel XR™

quetiapine

One for All



Atypical one-for-all power

Proven efficacy and tolerability in schizophrenia, bipolar disorder, MDD and GAD[1-10]

- Fast onset of action [4-8]
- Broad-spectrum improvement [1-10]
- Prevention of recurrence [1,3,9,10]

References: 1. Seroquel XR Package Insert Version July 2011. 2. Kahn RS et al. J Clin Psychiatry 2007; 68: 832-842. 3. Peuskens J et al. Psychiatry 2007; 4 (11): 34-50. 4. Cutler A et al., Clin Ther 2011; 33: 1643-1658. 5. Suppes T et al. J Affect Disord 2010; 121: 106-115. 6. Cutler A J et al. J Clin Psychiatry 2009; 70(4): 526-539. 7. Bauer M et al. J Affect Disord 2010; 127: 19-30. 8. Bandelow B et al. Int J Neuropsychopharmacol 2010; 13: 305-320. 9. Liebowitz M et al. Depression and Anxiety 2010; 27: 964-976. 10. Katzman MA et al. Int Clin Psychopharmacol 2011; 26: 11-24.

Abbreviated Prescribing Information:

Presentation: Quetiapine fumarate extended-release tablet. Indications: Bipolar Disorder: Maintenance treatment of bipolar I disorder, as monotherapy or in combination with lithium or sodium valproate, for the prevention of relapse/recurrence of manic, depressive or mixed episodes. Treatment of depressive episodes associated with bipolar disorder; Treatment of acute mania associated with bipolar I disorder as monotherapy or in combination with lithium or sodium valproate Schizophrenia: Treatment of schizophrenia, prevention of relapse and maintenance of clinical improvement during continuation therapy. Major Depressive Disorder: Treatment of recurrent major depressive disorder (MDD) in patients who are intolerant of, or who have an inadequate response to alternative therapies. Generalised Anxiety Disorder: treatment of generalized anxiety disorder (GAD). Dosage: Once-daily Schizophrenia: Initial dose: 300 mg (Day 1), 600 mg (Day 2) and up to 800 mg after Day 2. Range 400-800 mg/day depending on clinical response & tolerability of patient. Same dosage is used for maintenance therapy. Bipolar Disorder: Acute Mania: Starting daily dose is: 300 mg (Day 1) & 600 mg (Day 2) & up to 800 mg (after Day 2), alone or in combination with a mood stabilizer. Range 400-800 mg/day. Bipolar Depression: Starting dose is 50mg (Day 1) & 100 mg (Day 2) & 200 mg (Day 3) & 300 mg (Day 4). Titration can be up to 400 mg on Day 5 and up to 600 mg by Day 8. Maintenance treatment: Use same dose as active treatment for prevention of manic, depressive or mixed episodes in bipolar disorder. Range: 300-800 mg/day. Recurrent major depressive disorder: Once-daily in the evening. Initial dose: 50 mg (Day 1 & 2), increased to 150 mg on Day 3 & 4. Usual effective dosage: 150 mg. Range of 50 – 300 mg/day. Same dosage is used for maintenance. Generalised Anxiety Disorder: Initial dose: 50 mg (Day 1 & 2), increased to 150 mg on Day 3 & 4. Range of 50 – 150 mg/day. Switching from Seroquel IR: Switch at equivalent total daily dose. Individual adjustments may be necessary. Elderly: Initial dose: 50 mg/day up to target dose depending on clinical response and tolerability of patient. Slower dose titration is recommended. Elderly MDD: Initial dose: 50 mg (Day 1-3), increased to 100 mg (Day 4), 150 mg (Day 8) and then up to 300 mg. Elderly GAD: Initial dose: 50 mg (Day 1-3), increased to 100 mg (Day 4), up to 150 mg on day 8. Patients with hepatic impairment: Initial dose: 50 mg/day up to target dose. Patients with renal impairment: No dosage adjustment needed. Contraindications: Hypersensitive to the active substance or excipients of this product. Precautions: Not recommended for below 18y old; Clinical worsening and suicide risk associated with psychiatric disorders; Somnolence; Severe neutropenia; Known cardiovascular & cerebrovascular disease; Conditions predisposing to hypotension; Orthostatic hypotension; Extrapyramidal symptoms; History of seizures; Tardive dyskinesia; Neuroleptic malignant syndrome; not approved in elderly patients with dementia-related psychosis; Established diabetes mellitus; Dysphagia; Jaundice development; Venous thromboembolism; Galactose intolerance; Pregnancy & lactation. Interactions: CYP3A4 inhibitors; centrally acting drugs; grapefruit juice thioridazine; lorazepam; levodopa and dopamine agonists; carbamazepine, phenytoin, ketoconazole; ADHD medications & cardiovascular medicines that cause electrolyte imbalance or to increase QTc interval. Undesirable effects: Tachycardia; vision blurred; mild asthenia; peripheral edema; irritability; increased appetite; dysarthria; elevations in serum transaminases (ALT, AST), syncope; rhinitis; abnormal dreams & nightmares and elevations in serum prolactin. Full local prescribing information is available upon request. APLHK.SXR.0711

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31.210.022 02/08/2013

Message from the President

As we receive the July issue of the Journal, we have passed the first half of 2014. Earlier this year we saw the excellent work in the January issue on haematology by Dr Au Wing Yan, and the March issue on rheumatology by Dr Chan Tak Hin, as well as the informative articles by various authors in the June issue. In this July issue you will be able to read interesting articles on Alzheimer's disease, Robots in Neurological Rehabilation and Atrial Fibrillation. I am thankful to the various editors and contributors whose dedication have made the publication successful.

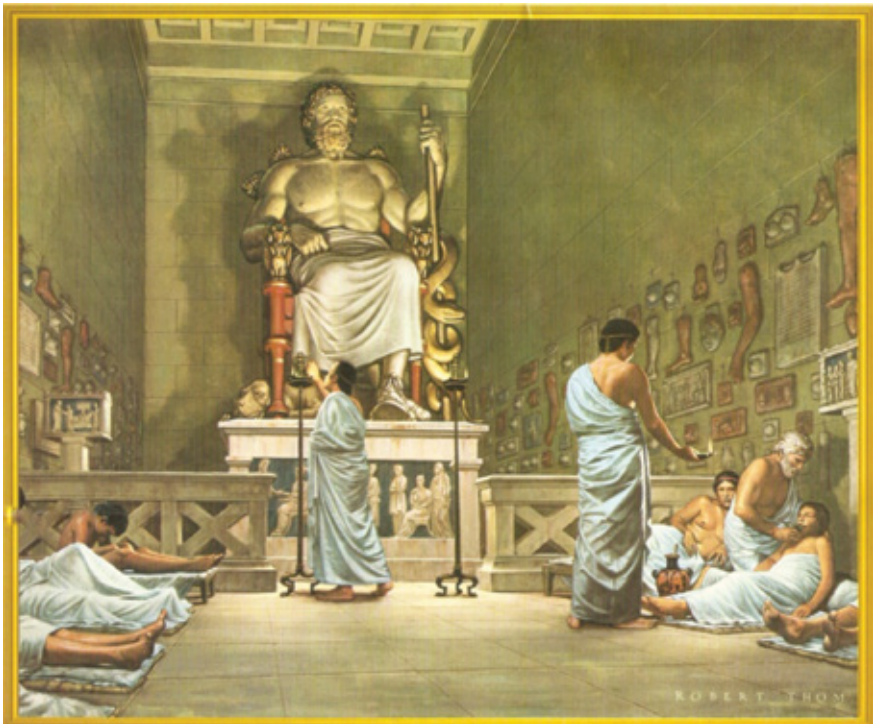
I would like also to welcome Professor Tse Hung Fat to the Editorial Board. Professor Tse will be in charge of the cardiology section and you will soon be able to benefit from his insights.

The Society has offered many interesting meetings in the first half of the year and I can promise that there will be even more exciting programmes to come in the latter half. Please look out for our programmes and I do hope to meet with you at our meetings.

Dr Lam Tat Chung, Paul
林達聰醫生

FRCP, FHKAM (Medicine)
FRCPsych, FHKAM (Psychiatry)
President

Pictorial Medical History (9)



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Specialist in Psychiatry (Private Practice)
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The University of Hong Kong

THE CULT OF ASCLEPIUS

As Asclepius became famous and his influence spread, he attracted a great number of followers which formed the Cult of Asclepius (this is where myth ends and history starts). The Asclepiadae were priest-healers who practiced medicine in Greece and around the Mediterranean. They were a highly respected group in the society and were given many privileges. They built healing temples where the sick travelled to seek treatment.

(Note the rod with one snake held by the statue of Asclepius and the votive offerings on both walls)

Advances in Alzheimer's Disease

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Key words:
Alzheimer's disease (阿滋海默氏症), Dementia risk & prevention (老年癡呆症的風險與預防), Rivastigmine patch (Rivastigmine 貼片)

A survey in Hong Kong has shown that more than 6% of people over 70 years old suffer from dementia,[1] with the majority of patients experiencing Alzheimer's disease (AD) (Fig 1). As the local and world population gets more advanced in age, AD will exert a heavy demand on doctors and healthcare services.

Current medications for the treatment of AD aim at boosting the neurotransmitter acetylcholine in the brain by inhibition of acetylcholinesterase, and there are several such medications in current use. However, more recent research also emphasizes the importance of inhibition of butyrylcholinesterase, another enzyme involved in the degradation of acetylcholine. Of the currently available drugs, rivastigmine is the only one that inhibits both acetylcholinesterase and butyrylcholinesterase.[2] Nordberg et al examined the cholinesterase inhibitor effect of different drug on cerebrospinal fluid (CSF) cholinesterases in patients with AD.[3] They found that rivastigmine had a much stronger inhibition of acetylcholinesterase than other drugs in the same class. Furthermore, rivastigmine has a low potential for drug-drug interaction as it is degraded by hydrolysis, whereas donepezil and galantamine are metabolised by cytochrome CYP450 isoenzymes. When using vagotonic agents, possible side effects include bradycardia, heart block, syncopy or lowering of blood pressure. In clinical trials, rivastigmine was not associated with any increased incidence of cardiovascular adverse events, heart rate, blood pressure changes or electrocardiography (ECG) abnormalities.

Rivastigmine skin patch

Advances in treatment have also been realized by the development of the rivastigmine transdermal patch. The patch is applied daily with a starting dose of 4.6 mg/24 hour, and after 4 weeks increased to 9.5 mg/24 hour if well tolerated. This form of delivery has the advantage of keeping drug levels in an optimal therapeutic

Figure 1. Distribution of dementia cases

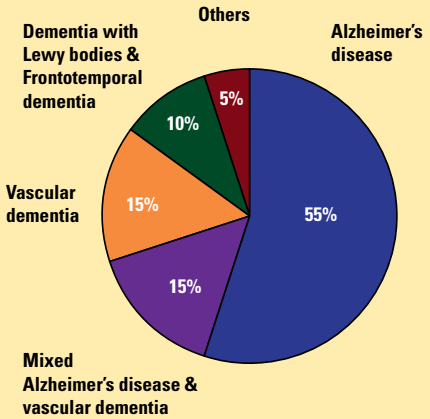


Figure 2. Pharmacokinetics: Smooth, continuous delivery by transdermal patches keeps drug levels in optimal "therapeutic window"

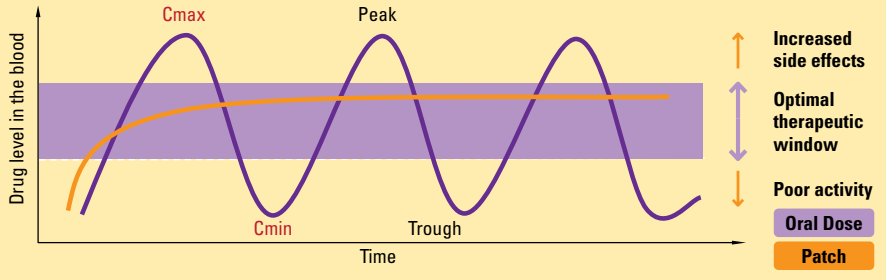
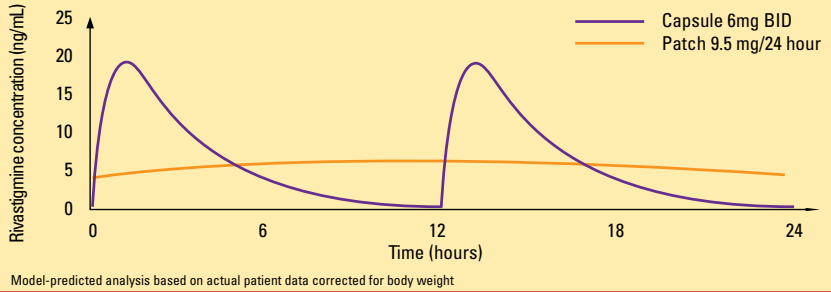
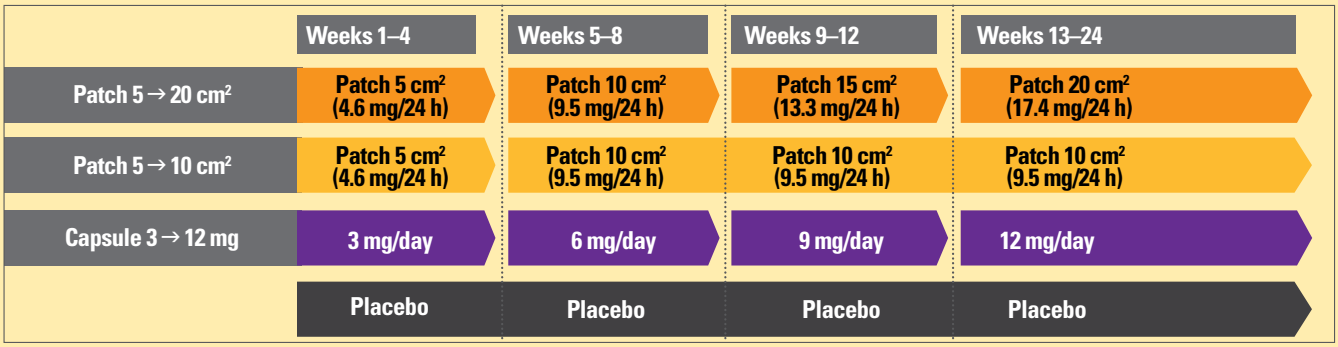


Figure 3. Rivastigmine transdermal patch provides smooth continuous delivery through the skin



Model-predicted analysis based on actual patient data corrected for body weight

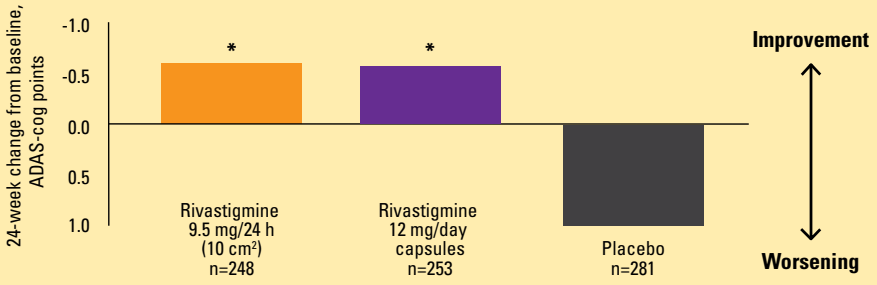
Figure 4. IDEAL study: To compare the efficacy, safety and tolerability of rivastigmine patch versus capsule in patients with AD



window, thus avoiding the increased side effects during a peak blood level and the poor efficacy associated with a low blood level (Fig 2).[4] The rivastigmine transdermal patch provides smooth continuous delivery through the skin, and is a favoured advance compared with the irregular delivery from the oral form of medication (Fig 3).[5,6]

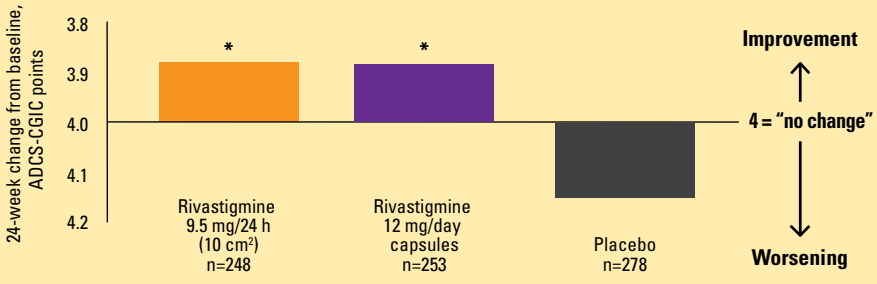
The Investigation of transDermal Exelon in ALzheimer's disease (IDEAL) study set out to compare the efficacy, safety and tolerability of rivastigmine patch versus capsule in patients with AD.[7] It was a 24-week randomized, multi-national, double-blind, double-dummy study involving 1,195 patients aged 50–80 years with probable AD, baseline Mini-Mental State Examination (MMSE) scores 10–20 inclusive. Patients were assigned to four groups; group 1 received patches of increasing doses, group 2 received patches up to 9.5 mg/24 hour, group 3 received an increasing dose of oral rivastigmine and group 4 received placebo (Fig 4). Using the Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog), rivastigmine patch was shown to be superior to placebo, and at least as effective as capsule on cognition (Fig 5). The Alzheimer's disease Cooperative Society-Clinician Global Impression of Change (ADCS-CGIC) scale was used to measure global impression and rivastigmine patch was demonstrated to be superior to placebo (Fig 6). Measuring functional outcomes by the Alzheimer's Disease Cooperative Society-Activities of Daily Living (ADCS-ADL) scale again demonstrated rivastigmine patch was superior to placebo (Fig 7).[7]

Figure 5. ADAS-cog: Rivastigmine patch superior to placebo, at least as effective as capsule on cognition[7]



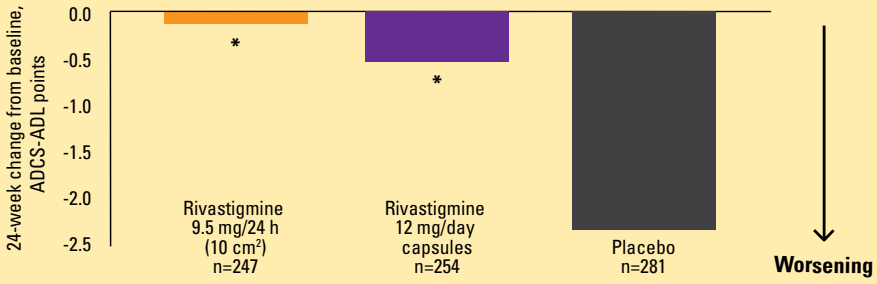
ITT-LOCF analysis
*p<0.05 versus placebo

Figure 6. ADCS-CGIC: Rivastigmine patch superior to placebo on global impression[7]



ITT-LOCF analysis
*p<0.05 versus placebo

Figure 7. Functional outcomes (ADCS-ADL): Rivastigmine patch superior to placebo[7]



ITT-LOCF analysis
*p<0.05 versus placebo

Rivastigmine patch was superior to placebo and at least as effective as maximum capsule dose as measured by the MMSE (Fig 8a). In the trail-making test, rivastigmine 9.5 mg/24 hour patch improved attention versus placebo (Fig 8b). The main adverse effects of cholinesterase inhibitors are nausea and vomiting, this was found to be significantly reduced by using the rivastigmine patch compared with capsule (Fig 9).[7] Compliance improved from 64.4% with capsules to 95.9% with patch, and caregiver preference significantly favoured the transdermal patch.[7]

In the area of activities and behaviour, rivastigmine patch treatment improved both instrumental and basic activities of daily living.[8] It also improved behavioural symptoms including attention, anxiety, apathy and agitation in both outpatients and institutionalized patients and allowed reduction in dose of antidepressants, antipsychotics, anxiolytics, hypnotics and mood stabilizers.[9]

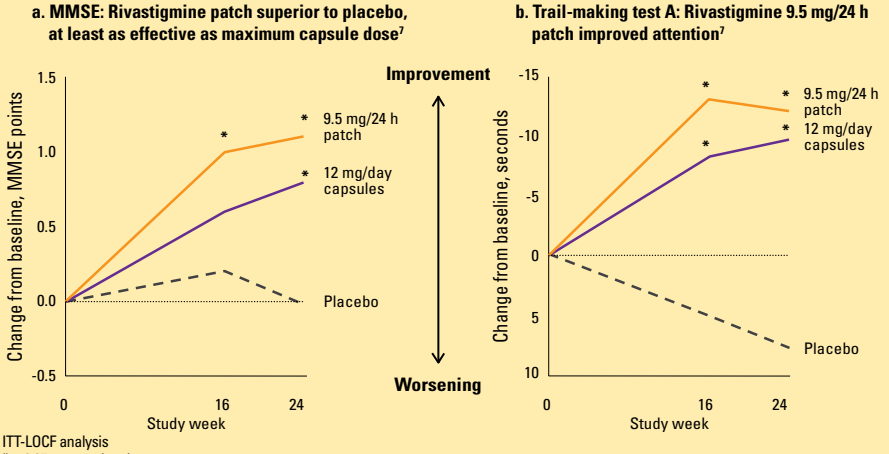
Studies have shown that high-dose early treatment with acetylcholinesterase inhibitors, including rivastigmine, are important to optimize long-term outcomes for patients with AD. Initiating therapy later in the disease course does not enable patients to "catch up" with the functional or cognitive ability of those patients whose treatments were initiated earlier.[10]

Scanning for amyloid

As it has been observed that the brains of patients with AD contain deposits of amyloid protein, it would be an advantage if the density of such amyloid deposits could be studied during the patient's life.

Pittsburg compound B (PiB) was the first substance used with some success in the scanning for brain amyloid. However, it has a short radioactive half-life of 20 minutes and so is inconvenient in practice, it has to be used immediately after generation from a cyclotron. The first scanning agent, which was approved by the FDA in 2012, was florbetapir (Amyvid, Lilly), which has a half-life of 110 minutes. Since then, a second agent, flutemetamol (Vizamyl,

Figure 8.



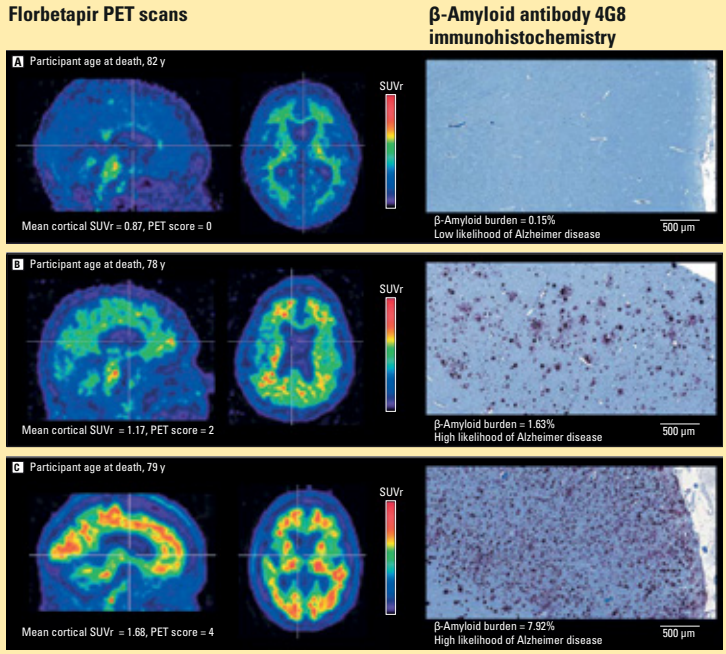
ITT-LOCF analysis
*p<0.05 versus placebo

Figure 9. Safety and tolerability: Rivastigmine patch reduces adverse events

	Rivastigmine10 cm² patch (n=291)	Rivastigmine capsule (n=294)	Placebo (n=302)
Any AE	147 (50.5%)	186 (63.3%)	139 (46.0%)
Nausea	21 (7.2%)	68 (23.1%)	15 (5.0%)
Vomiting	18 (6.2%)	50 (17.0%)	10 (3.3%)
Diarrhoea	18 (6.2%)	16 (5.4%)	10 (3.3%)
Weight decreased	8 (2.7%)	16 (5.4%)	4 (1.3%)
Dizziness	7 (2.4%)	22 (7.5%)	7 (2.3%)
Decreased appetite	2 (0.7%)	12 (4.1%)	3 (1.0%)
Headache	10 (3.4%)	18 (6.1%)	5 (1.7%)
Asthenia	5 (1.7%)	17 (5.8%)	3 (1.0%)

Events occurring in at least 5% of patients in any treatment group

Figure 10. Paired representative florabetapir-PET scans and β-Amyloid antibody 4G8 immunohistochemistry photo micrographs



Sagittal and axial views of positron emission tomographic (PET) scans of representative patients. The vertical bars indicate the range of semiautomated quantitative analysis of the ratio of cortical to cerebellar signal (S-Vr) scores. The maximum color (red) corresponds to an SUVr of approximately 2.2. The 4G8 immunohistochemistry shows precuneus gray matter with aggregated β-amyloid (red) using a 3-amino-9-ethyl-carbazol chromogen stain and counterstained with acid blue 129 (original magnification x5).

GE Healthcare) was approved in Oct 2013 and more recently Florbetaben (Neuraceq, Piramal) was approved in March 2014.

A study was undertaken to determine if florbetapir positron emission tomographic (PET) imaging performed during life accurately predicts the presence of ß-amyloid in the brain at autopsy. Florbetapir-PET imaging was performed in 35 patients near the end of their lives (mean 99 days before death). These scans were compared with autopsy studies for amyloid. Florbetapir-PET images and postmortem results rated as positive or negative for ß-amyloid agreed in 96% of cases analysed. Florbetapir-PET imaging also correlated with the density of ß-amyloid (Fig 10).[11]

The Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging (SNMMI), USA, estabilised an Amyloid Imaging Task Force, which released a practice guideline in 2013. Scenarios for appropriate and inappropriate use are shown in Call-out box 1 and Fig 11.

Anaesthesia and dementia risk

A study in Taiwan looked at the Taiwan National Health Insurance Database to assess anaesthesia and dementia risk. The cohort consisted of patients under 50 years old who were anaesthetized for the first time between 2004–2007. The cohort was followed up for 2–7 years. Six hundred and sixty one of 24,901 patients developed dementia (2.65%), mainly AD. Of the control group, 1,530 of 110,922 patients developed dementia (1.39%). There was a doubling of risk for patients who had undergone anaesthesia.[12]

Statins and dementia risk

There have been controversies regarding the effects of statins on dementia risk. Lin et al from the National Taiwan University Hospital reviewed 1 million patients covered by the Taiwan National Insurance Database. They identified 57,669 patients over 65 years with no history of dementia in 1997–1998 and followed up for 4.5 years. Of these, 15,200 patients were taking statins, and patients not taking statins were used as control. There were 5,516 cases

Call-out box 1

Amyloid imaging is appropriate for individuals with all of the following characteristics:

- **Cognitive complaint with objectively confirmed impairment**
- **Alzheimer's disease a possible diagnosis, but the diagnosis is uncertain after a comprehensive evaluation by a dementia expert**
- **When knowledge of the presence or absence of Aβ pathology is expected to increase diagnostic certainty and alter management**

Figure 11. Appropriate and Inappropriate scanning scenarios

Scenarios when scanning is appropriate

1. **Patients with persistent or progressive unexplained mild cognitive impairment**
2. **Patients satisfying core clinical criteria for possible Alzheimer's disease because of unclear clinical presentation; ie, either atypical clinical course or etiologically mixed presentation**
3. **Patients with progressive dementia and atypically early age of onset (usually defined as ≤65 years)**

Scenarios when scanning is inappropriate

1. **Patients with core clinical criteria for probable Alzheimer's disease with typical age of onset**
2. **To determine dementia severity**
3. **Solely based on a positive family history of dementia or presence of ApoE Ɛ4**
4. **Patients with a cognitive complaint that is unconfirmed on clinical examination**
5. **In lieu of genotyping for suspected autosomal mutation carriers**
6. **In asymptomatic individuals**
7. **Nonmedical usage (eg, legal, insurance coverage, or employment screening)**

of AD detected and the risk for dementia was found to be lower with higher dose of statins, and also with the use of stronger statins like atorvastatin and rosuvastatin (Fig 12). Lovastatin was associated with higher risk. This is the first large scale, nationwide study to examine the effect of different statins on new onset nonvascular dementia in an elderly population.[13]

In another study by Liou et al, also from the National Taiwan University Hospital, 5,221 patients with atrial fibrillation were followed up for 6 years and 1,652 were taking statins. Of the statin group, 2.1% developed dementia compared with 3.5% in the non-statin group. There was a 44% reduction in dementia risk in the statin group.[14]

Gammaglobulin Alzheimer Partnership (GAP)

In this phase 3 study, 390 patients from US and Canada with mild-to-moderate AD were treated with 36 infusions of intravenous immunoglobulin or a placebo albumin infusion every two weeks over 18 months. There was no significant improvement in the treatment group compared with the placebo group as measured by the ADAS-cog subscale and the ADCS-ADL.[15] Therefore, this can be considered to be a negative study; however, certain benefit can be seen in specific subgroups. Favourable changes were shown in the Modified MMSE and Trail B test in Apo E4 patients and moderately impaired patients. There was a decrease in plasma Aß 42 (not in Aß 40), decrease in brain fibrillar amyloid by florbetapir scan, especially in Apo E4 carriers and increase in anti-oligomer and anti-fibril antibodies in the plasma and CSF.

Prevention

In 2012, the World Health Organization (WHO) declared dementia to be a public health priority. Efforts aimed at prevention or delaying the onset of the condition will be of great importance to alleviate the disease burden.

1. **Exercise.** There is strong evidence of the protective effects of exercise in AD. Active animals have larger hippocampi, and people who walk regularly have a lower risk of developing AD. People who exercise have larger brains, better cognitive ability, lower amyloid burden, reduced CSF tau and increased CSF amyloid (associated with a lower risk for AD).
   a. A recent study from Spain studied 22 non-demented elderly subjects prescribed 15 minutes of daily stationary cycling for 15 months, 17 patients without aerobic exercise were used as the control group. The study group was found to have improved global cognitive status and psychomotor speed, but no improvement for tests on memory and learning.[16]
   b. Women with mild cognitive impairment were assigned to do 1 hour of training twice a week. Group 1 participated in resistance training, group 2 in aerobic training and group 3 in balance and tone. At the end of the 6 month programme, hippocampal volume was measured by MRI. The researchers found a 4% increase in total hippocampal volume in the aerobic training group, which was significantly increased compared with the other groups.[17]
   c. A Cochrane Library review published in Dec 2013 examined 16 trials involving 937 patients with dementia. It concluded that exercise had a beneficial effect on cognition and activities of daily living.[18]
   d. Researchers from Washington University, St. Louis studied 201 cognitively normal adults. Subjects were classified into high-exercise group and low-exercise group. Sedentary subjects were found to have higher amyloid load and lower CSF Aß 42 (indicating higher risk for AD).[19]
2. **Mental stimulation** is believed to delay or prevent AD. Two recent studies are of interest:
   a. A study from France used data from the Health & Pension Database; 429,803 self-employed workers who were living and retired as of Dec 31, 2010 were included. Of the group, 11,397 had dementia (2.65%). For each extra year of age at retirement, the risk of dementia was 3.2% lower. People retiring at age 65 had a 14.6% lower risk than those retiring at age 60.[20]
   b. A study from Hyderabad, India, studied 648 individuals with dementia, 391 of whom were bilingual. Bilingual patients developed dementia 4.5 years later than those who spoke only one language. Hyderabad was especially suited for this kind of study because the population was homogenous, unlike previous studies from Toronto, Canada where there was a

Figure 12. Risk for dementia with various statins by dosage tertiles

Statin	Lowest-dose tertile (Hazard ratio)	Mid-dose tertile (Hazard ratio)	Highest-dose tertile (Hazard ratio)	p value for trend
✔ Atorvastatin	0.680	0.543	0.305	<.001
✔ Rosuvastatin	0.365	0.134	0.129	.011
Fluvastatin	0.971	0.578	0.255	.058
Simvastatin	0.747	0.644	0.510	.064
Pravastatin	0.662	0.933	0.491	.422
X Lovastatin	1.382	0.930	1.626	.116
All statins	0.923	0.806	0.311	<.001

large immigrant population with different backgrounds. Also, the level of education between the bilingual and monolingual groups was similar in the Indian study.[21]

3. **Psychological stress and AD.** Two reports can be quoted from recent literature:
   a. A Swedish study recruited 1,462 females aged 38–60 and performed a baseline examination in 1968–1969. They were followed up 6 years, 12 years, 24 years and 35 years later and 161 cases had developed dementia. Those subjects reporting frequent/constant stress in one follow up had a hazard ratio of 1.1, those reporting stress in 2 follow ups 1.73 and those reporting stress in 3 follow ups 2.51.[22] The same team studied 800 women followed up for 38 years with 153 cases developing dementia. The subjects reported on 18 psychological stress factors including mental illness in relatives, berevement, divorce and unemployment. The Authors concluded that psychological stress factors were associated with higher incidence of AD (hazard ratio 1.20).[23]
   b. A study from Argentina examined the effect of stress on the onset of AD, 118 patients with AD were compared with 81 controls. Of the patients, 72% experienced severe stress in the 2 years before the onset of symptoms compared with 26% of control subjects. The authors postulated that stress can trigger a degenerative process in the brain and precipitate dysfunction in the neuroendocrine and immune systems.[24]

Diet and AD

a. In July 2013 the Physicians Committee for Responsible Medicine in the US published "The seven dietary principles to reduce AD risk" (Fig 13).[25] Although there are some criticisms that the report is not fully evidence based, it can serve to remind us of a healthy lifestyle and eating habit.
b. A study from the University of Eastern Finland in 2014 showed that those who ate the most healthy diet (fish, nuts, fruit and vegetables) at the average age of 50 had a 90% risk reduction of dementia in a 14 year follow up than those who ate the least healthy diet (eggs, saturated fats, sausages) using a healthy diet index.[26]

Figure 13. The seven dietary principles to reduce Alzheimer's risk

1. **Minimize saturated fats and trans fats**
2. **Vegetables, legumes (beans, peas, and lentils), fruits, and whole grains should be the primary staples of the diet**
3. **One ounce of nuts or seeds (one small handful) daily provides a healthful source of vitamin E**
4. **A reliable source of vitamin B12, (such as fortified foods or a supplement providing at least 2.4 µg per day for adults) should be part of the daily diet**
5. **Choose multivitamins without iron and copper, and consume iron supplements only when directed by your physician**
6. **Avoid the use of cookware, antacids, baking powder, or other products that contribute dietary aluminium**
7. **Engage in aerobic exercise equivalent to 40 minutes of brisk walking 3 times per week**

Conclusion

In 2010 the world estimate of patients with AD was 35 million. The number will double every 20 years, to 65.7 million in 2030 and 115 million in 2050.[27] Physicians should contribute their best efforts for the research, treatment and care of this group of patients.

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Robotics in Rehabilitation

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Key words:
Robotics (機械人), Rehabilitation (復康)

Introduction

Robotics is science that deals with robots, these are automated machines that can take the place of humans or resemble humans in appearance, behavior and/or cognition. Initial applications of robotics in the field of medicine were for rehabilitation devices and assistance for those with disabilities. Another term "bionics" can be considered under the umbrella of robotics. Bionics is the application of biological methods and systems found in nature to the study and design of engineering related to humans. It has been popularized by sci-fi movies like "Iron Man". The products are not mere prostheses which closely mimic the original function; they have the capability to surpass them. Bionics are not the topic of discussion here, though technology has advanced dramatically they are still far from ideal and cannot replace human body parts, at least in the foreseeable future. We treasure our human bodies as engineering marvels and in the unfortunate event of stroke or brain damage, the goal is to revert to the original function and this can be attained through rehabilitation. Robotics has led to remarkable developments in rehabilitation in recent years.

In stroke survivors, 20% need institutional care at 3 months and 15–30% are left with permanent disabilities. The aims of post-stroke rehabilitation are: to promote recovery of lost function and to allow independence and early reintegration into social and domestic life.

The most effective rehabilitative interventions are those which provide early, intensive, task-specific, and multi-sensory stimulation. The brain's adaptation to damage is influenced by sensory input, experience and learning. Neural plasticity indicates the recovery mechanisms and functional adaptation resulting from global changes in structural organization. Neural adaptation leads to a more robust recruitment of motor neuron pools, transfer of function from damaged areas to preserved adjacent or correlated areas, strengthening of redundant or parallel synapses, new synapse formation, increased dendritic sprouting, enhanced myelination of remaining neurons, and modification of cortical and noncortical representations. Recently, the cerebellum has been seen to play a key role in modulating cortical motor output and in motor learning. Hence, although neural damage cannot be replaced by cellular proliferation, partial compensation might be provided by adaptive mechanisms, including variations in neural schemes through the unmasking of hidden neural pathways and synapses which, although not normally used, might emerge when the dominant system fails. Currently available literature advocates a strong relationship between intense multisensory rehabilitation and recovery in stroke patients. Thus, well-defined training methods, implementing intense multisensory stimulation, may induce neural adaptations and enhance motor and functional recovery of the paretic upper extremity. The use of automatic devices was proposed to help therapists increase the intensity of therapies, produce multisensory stimulation, and reduce costs during their work.

The worldwide annual costs of neurorehabilitation are staggering, exceeding US$ 400 billion. Stroke, traumatic brain injury and other neurological disorders are costly diseases from human, familial and societal perspectives. The global market for robotic devices and rehabilitation systems increased from US$ 602 million in 2010 to over US$ 1 billion in 2012, with a remarkable compound annual growth rate of 34%. While being one of the fastest growing markets in the neuro-technology field, the market is far from exhausting its potential which is estimated at US$ 15 billion.

Types of machines

In recent years, robotic devices have been widely used to replace manpower and physical need of therapists in the field of neurological rehabilitation. It increases the amount of exercise patients with nerve damage receive. The currently available robotic devices can be divided into two main categories: those for the upper limb and those for the lower limb. Robotic rehabilitation devices can also be classified into exoskeleton robot, and end-effector robot (Fig 1). Exoskeleton robot is the most widely utilized rehabilitation robotic system in the field of gait training. This system is commonly used to improve gait function of patients with lower limb disorders. The structure is composed of exoskeleton leg, treadmill and suspension system (Fig 1a). The end-effector robot was designed in reference to the programmable footplate concept. Each of the two manipulators comprise a hybrid serial-parallel robot and a footplate

Figure 1. Illustrations of two types of lower limb robotics: (a) exoskeleton (b) end-effector

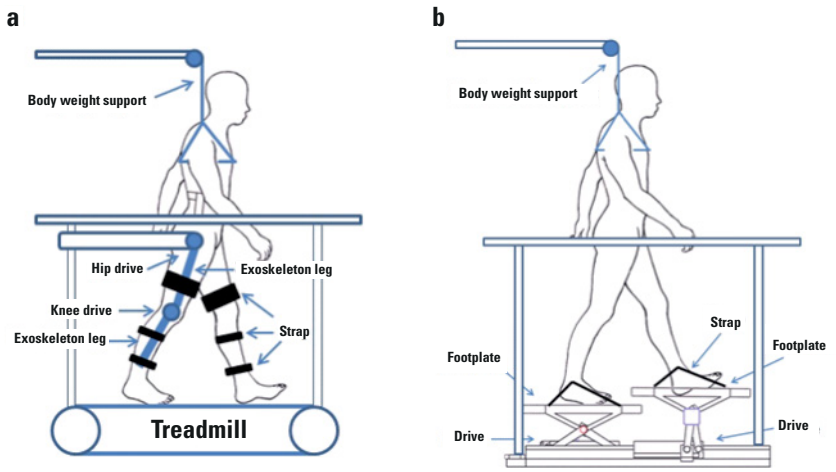
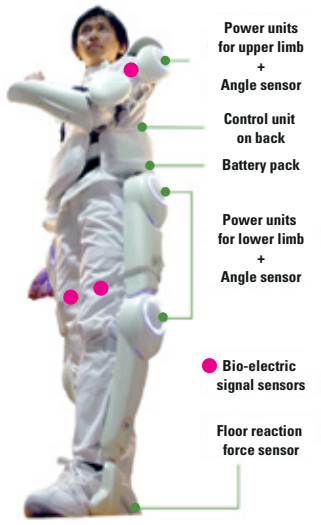


Figure 2. Hybrid Asistive Limb. Can assist or even augment limb function



for permanent foot attachment at its end-effector. The subject's feet are fixed to the footplates via safety release; the step length, step frequency, step height and step speed can be adjusted according to the patients' gait ability on end-effector robot (Fig 1b).

A few commercially available systems have been chosen to illustrate this state-of-the-art technology:

1. Japan is renowned for robot technology. The Hybrid Assistive Limb (HAL) is a powered exoskeleton suit developed by Japan's Tsukuba University and the robotics company Cyberdyne (Fig 2). It has been designed to support and expand the physical capabilities of its users, particularly people with physical disabilities. It can be viewed as a bionic rather than rehabilitation tool. Hospital trials of the full HAL suit began in 2012, with tests to continue until 2015. By October 2012, HAL suits were in use by 130 different medical institutions across Japan. In February 2013, the HAL system became the first powered exoskeleton to receive global safety certification. In August 2013, HAL received EC certification for clinical use in Europe as the world's first medical-treatment robot.
2. The bionic leg (Fig 3) provides intent-driven and/or adjustable robotic assistance to the patient's affected limb when attempting to stand, sit, walk, or ascend and descend stairs. There are sensors under the sole, over the calf and on the thigh. When a preset pressure is sensed, the robotic limb will flex and extend, mimicking normal leg movements. It improves patients day-to-day capabilities by enabling higher-level balance exercises, gait training and strengthening exercises. It also reduces the need for additional therapist assistance during exercises, allowing the clinician to focus on the patient and the quality of the movement.
3. Anti-gravity treadmill (Fig 4). In essence, this supports the patient's weight above the waist while allowing him or her to walk on the treadmill. It can be used for:
   - Rehabilitation following an injury or surgery on a lower extremity (hip, knee, ankle or foot)
   - Rehabilitation after total joint replacement

Figure 3. Bionic leg. Helping the patient to restore normal leg functions of standing, walking and climbing stairs

Figure 4. Anti-gravity treadmill. Allowing patients to walk without the weight of trunk and upper limbs

Figure 5. Functional electrical stimulation of hand with wireless control

- Gait training and strengthening for neurological patients
- Strengthening and conditioning in a fall-safe environment for older patients
- Weight-loss programs
- Injury prevention during sport-specific conditioning and fitness improvement programs

4. Hand Rehabilitation System (Fig 5). This employs the functional electrical stimulation principle. Low voltage long duration electrical stimulation is delivered to the forearm muscles to produce movements like grasping or opening of the hand. It supports the wrist in a functioning position, allowing the fingers and thumb to move efficiently. It has two main components: the functional stimulation support (orthosis) and the wireless control unit (microprocessor) and is intended to:

- Improve ability to perform activities of daily living
- Reduce muscle spasms
- Improve voluntary movement of the hand and wrist
- Re-educate muscles over times

Additionally, the system may reduce or prevent secondary complications, maintain or increase range of motion, increase local blood circulation and prevent or decrease muscle atrophy.

Advantages of robotics in rehabilitation

Robotic technology represents a feasible tool to administer treatment protocols with the characteristics of intense, highly repetitive, and task-oriented movements. Specifically, they provide therapy for long time periods, in a consistent and precise manner, maximizing efficiency for both the patient and therapist. They are programmed to perform in different functional modes and can be automated for many functions; they can also measure and record a range of behaviors corresponding to specific therapeutic applications.

Robotics can also generate a more complex, controlled multisensory stimulation of the patient. Studies observed that interhemispheric connectivity between primary somatosensory areas got closer to a "physiological level", after a robot-assisted rehabilitation program, alongside the acquisition of more accurate hand control. With regards to the lower limb, recent studies have demonstrated better outcomes after repeated walking programs with growing intensities. The repetitive execution of complex gait cycles for these patients requires specific devices such as the treadmill, with and without partial body weight support. Treadmill training requires a considerable effort by the therapist to set the paretic limbs and to control weight shift and this may limit therapy intensity, especially in more severely disabled patients. In order to reduce dependence on therapists, gait machines consisting of either an electromechanical solution with two driven foot plates simulating the phases of gait, or a robot-driven exoskeleton orthotic are helpful.

The unknowns

Unfortunately, the majority of the existing robotic devices for neurorehabilitation were designed and programmed to produce simple stereotypical movement patterns, often not related to functional activities. The aim of simpler technology is to promote the widespread use of more economic and easier robotic devices which could be used for home therapy. Conversely, the creation of more sophisticated devices allowing a full range of motion could improve functional outcomes and in the future, it is hoped that the equipment can have both these advantages.

There are inadequate large-scale studies to demonstrate the efficacy of robotics. The studies are difficult to conduct due to the variability in different machines. In the past, studies were mainly undertaken on chronic patients. In the acute or subacute phase of stroke, robotics may lead to a clinical improvement mainly due to the increased brain plasticity early after stroke. With advances in technology, future lightweight and wearable orthotic systems can make training more natural and ultimately release it from the confines of the rehabilitation field.

In conclusion, these machines are intended to represent an adjunctive tool to increase the intensity of therapies, in line with modern principles of motor rehabilitation. A robot can never replace the multilevel interactions between patient and experienced physical therapist or the manual ability of operators.

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An Update in the Management of Atrial Fibrillation

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Key words:
Atrial fibrillation (心房顫動),
Stroke prevention (預防中風),
Catheter ablation (導管消融術)

Atrial fibrillation (AF) is the most common sustained arrhythmia affecting 3–6 million people in United States and Europe,[1,2] and it is estimated that there are over 100,000 patients with AF in Hong Kong. The incidence of AF rises with age and the lifetime risk of AF development in those over 40 years old is around 25%.[3] AF does not solely affect elderly patients and its incidence in those aged under 60 years ranges from 0.5–1% of the general population.[4] It is expected that these figures will increase 2.5–3-fold in the next 50 years.[1,5] AF doubles the risk of death, increases the risk of stroke 5-fold and heart failure 3-fold. It adversely affects the prognosis of those with coronary artery disease,[6] heart failure[7] or even hypertension.[8] Management of AF is a complex issue and guidelines are available[9] but the adoption into clinical practice is challenging and limited by cultural, social and economic reasons.[10]

Sinus rhythm vs AF

Both patients and physicians frequently ask the same question regarding AF: Should we maintain sinus rhythm? The debate between rhythm or rate control has been ongoing for decades and lead to multiple randomized clinical trials to analyze whether rhythm control is superior to rate control in achieving better clinical outcomes.[11–17] These clinical trials demonstrated that both strategies were equivalent if cardiovascular events like mortality or stroke were chosen to be the primary endpoints. Proper anticoagulation and better symptomatic control, instead of rate or rhythm control strategies, are key to lower cardiovascular events in these patients. The clinical implications of these findings are emphasized in the management guidelines of AF.[9] The guidelines state that these strategies are not mutually exclusive and AF management should focus on a comprehensive treatment plan for each individual, including stroke prevention and symptomatic relief.

Stroke prevention in AF

Evaluation of the thromboembolic risk in AF patients is a top priority in the management algorithm.[9] The initial assessment tool is $CHADS_2$ score,[18] one point is assigned if the patient has Congestive heart failure, Hypertension, Age >75 years or Diabetes mellitus. Two points are given for previous history of Stroke or transient ischemic attack. It is a useful tool in the primary care setting as it can be easily remembered by physicians and does not require any sophisticated investigations. Patients classified as high risk for thromboembolism ($CHADS_2$ score ≥2) should receive oral anticoagulation (OAC) while those at low risk can receive either anti-platelet therapy or OAC. A more comprehensive assessment scheme is now available, CHA_2DS_2-VASc, which takes into account several previously underscored, but clinically important, predictors of stroke in patients with non-valvular AF, for example, age between 65–74 years (1 point), >75 years (2 points), female sex (1 point) and co-existing vascular disease (1 point).[2] It should not be considered a new tool, but rather an expanded version. OAC is still recommended for those with $CHADS_2$ score >2 but a detailed assessment with regards to these risk factors is necessary for those with $CHADS_2$ score 0 or 1. OAC is suggested for those with CHA_2DS_2-VASc score of 1 while no antithrombotic therapy is recommended for CHA_2DS_2-VASc score of 0. The new guidelines also stress the importance of bleeding risk assessment with the HAS-BLED scheme,[2] Hypertension, Abnormal renal or liver function (1 point each), Stroke, Bleeding episodes, Labile international normalized ratio (INR), Elderly (age >65 years) and Drugs (anti-platelet or non-steroidal anti-inflammatory drug) or alcohol (1 point each) with maximum of 9 points. Caution should be taken when prescribing OAC to those with HAS-BLED score ≥3.

Warfarin is the most commonly used OAC; however, its use has limitations including frequent INR monitoring, dietary restrictions and the potential for drug-drug interactions. These may lead to poor drug acceptance or compliance. Novel oral anticoagulants (NOACs) are as effective as warfarin in preventing stroke in patients with AF. NOACs include dabigatran, an oral direct thrombin inhibitor and rivaroxaban and apixaban, anti-factor Xa inhibitors.[19–21] Several large-scale clinical studies have demonstrated that NOACs are non-inferior to warfarin in

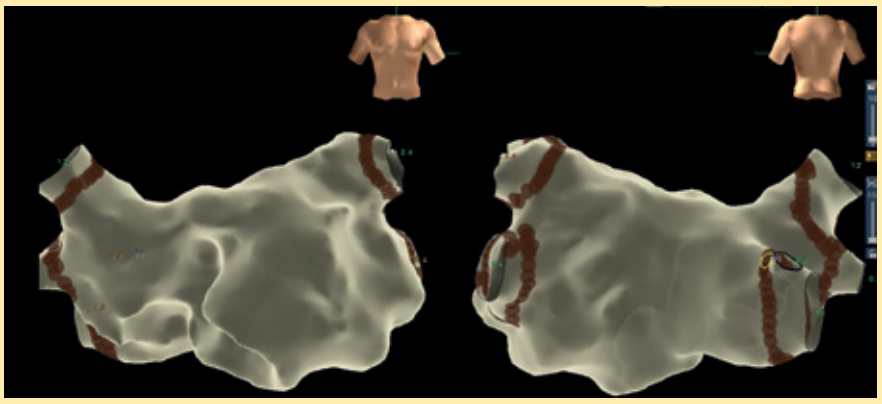
preventing stroke. More importantly, these NOACs do not require blood test monitoring for dosage titration and the risk of intracranial bleeding is significantly lower than that of warfarin.[22] They have all been approved by the Food and Drug Administration for stroke prevention in AF. Safety issues include lack of specific antidote, management of haemorrhage and optimal dosage for each individual. Long-term adverse effects with NOAC treatment remain unclear; however, they are a promising alternative to warfarin.[9]

Catheter ablation therapy for AF

Symptoms like severe palpitation, dizziness, dyspnoea and impaired exercise tolerance are common in patients with AF. In RECORD, an AF study, up to 76–85% of patients with AF were classified as having symptomatic AF. Previous studies have also demonstrated that the overall quality of life in patients with AF was lower than patients who had experienced myocardial infarction, reflecting the disruptive nature of the disease on daily living. Anti-arrhythmic drugs, including amiodarone, were ineffective in maintaining sinus rhythm with symptomatic recurrence in over 50% of patients. In addition, the significant side effects of these anti-arrhythmic drugs e.g. liver toxicity, lung fibrosis and thyroid disorder have limited their role in daily clinical practice.

Previous studies have shown that the trigger of AF is commonly a premature atrial complex (PAC) from the myocardial sleeves which wrap around the ostia of the pulmonary veins. Radiofrequency lesions can be delivered circumferentially to all four pulmonary veins after transseptal puncture to prevent the PAC from entering the left atrium and effectively control AF.[23–26] Advances in technology and 3-dimensional mapping have ensured the procedure time and success rate have improved substantially (Fig. 1). The procedure time has been shortened to 3–4 hours in experienced hands. Major complications including stroke, cardiac perforation and atrioesophageal fistula formation were low (<1%) in centres regularly performing this technique.[27] Multiple randomized clinical trials in drug-refractory patients have compared the efficacy of ablation versus medical therapy and have unequivocally demonstrated the superiority of ablation over medical therapy. Around 70–75% of patients remain AF free after 1 year of follow up. Moreover, the symptoms, frequency scores and quality of life as measured by SF-36, were consistently in favour of pulmonary vein isolation. As of 2006, AF ablation has been recommended for patients who remained symptomatic despite treatment, with at least one anti-arrhythmic drug. The role of catheter ablation as first-line therapy for symptomatic AF has been addressed in a recent randomized controlled trial.[28] This study randomized 127 treatment-naïve patients with AF to receive either anti-arrhythmic drug therapy or catheter ablation. A significant 44% risk reduction of AF recurrence was seen in the ablation group compared with the group receiving drug therapy. In the latest guideline, the procedure can also be recommended as the initial therapy for those with minimal or no structural heart disease, as the post-ablation outcomes are optimal in select patients, obviating the need for anti-arrhythmic drugs.[2]

Figure 1. Three dimensional mapping under Navigation and Visualisation Technology (NavX) guide



Left Anterior view of the left atrium showing circumferential radiofrequency lesions (brown dots) placed around the ostia of four pulmonary veins in a patient with paroxysmal atrial fibrillation.
Right Posterior view of the left atrium.

Conclusion

With the ageing population, there will undoubtedly be a growing number of patients suffering from AF. Stroke prevention remains the top priority in AF management algorithms according to the latest guidelines. Proper risk stratification schemes are available and should be routinely adopted into daily clinical practice. NOACs have great potential to replace the problematic vitamin K-dependent oral anti-coagulation drugs and will hopefully improve the adherence to evidence-based stroke prevention strategies for both patients and physicians. The lack of efficacy and related adverse effects has limited the role of anti-arrhythmic therapies in prevention of symptomatic AF recurrence, especially in young patients. Catheter ablation for AF is a preferred therapy for those with symptomatic AF despite anti-arrhythmic therapy and may be considered as first-line therapy for young patients or those with minimal structural heart disease, as they are expected to have the most favourable outcomes. Rate and rhythm control strategies are no longer mutually exclusive and consequently an individualized treatment plan is needed for patients with AF.

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A complete list of references can be downloaded from www.SOPHYSICIANSHK.org

OBITUARY

Dr Hans Tang (湯于翰醫生)

1913–2014

Dr Hans Tang, a native of Ningbo 寧波, was born in 1913. He studied medicine at the Medical School of 上海復旦大學 in Shanghai and graduated in 1934. He underwent postgraduate training in Belgium at the University of Louvain. In 1938 he was appointed to the post of Medical Superintendent of 上海鐳錠醫院 in Shanghai. In 1948 he became a Member of The Royal College of Physicians of Edinburgh and London, and was subsequently elected Fellow of the Edinburgh College in 1980, and the London College in 1988.

He was married in 1943 and settled in Hong Kong in 1945, shortly after the Second World War. In 1948 he began his private practice, specializing in Cardiology. At that time he was one of the few physicians in private specialist practice in Hong Kong. He was highly regarded by his patients and colleagues for his professionalism and humanitarianism. A tireless and influential professional, he played a significant role in facilitating the smooth operation of the Matilda Hospital. In fact, the Chinese name of the Hospital, 明德醫院, was coined by him.

In 1956, together with colleagues Dr Raymond Yang, et al. he founded the Society of Physicians of Hong Kong, an exclusive association of physicians in private practice with convivial monthly meetings over dinner, when presentations and discussions were held on topics of current interest not only in medicine, but in diverse other fields such as politics, economics, arts and entertainment.

In the 1990's, he spent a lot of time and energy on a very noble project – the establishment of a Medical School in the University of Ningbo. With his sage guidance and generous financial support, the Medical School was successfully inaugurated in 1997. This was probably the achievement he most treasured.

Besides being a prominent physician, Dr Tang was also a very successful businessman. This was no doubt a measure of his wisdom, acumen and ingenuity. For years he had been a strict vegetarian, not for religious or health reasons but for his belief in the motto 'Do not kill'. Despite being a workaholic, he was above all a family man. When he was struck by illness around ten years ago, he yearned to be able to live a little longer so that he could see more of his family.

He passed away peacefully on 25 May 2014. He is survived by his wife Nancy, daughters Joan and Ann, son Sherman, son-in-law Richard Chiu, daughter-in-law Ming Ho, grandchildren Warren Chiu, Carol Chiu and Clare Chiu, granddaughter-in-law Amanda and great-grandson Marcus Chiu.

For 101 years, Dr Tang lived gloriously and gracefully with enthusiasm, dedication, compassion, magnanimity and beneficence. His contribution to the medical field shall forever be cherished in our memory.

Dr Mak Lai Wo

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Exelon Patch 15 contains 27 mg rivastigmine. The release rate is 13.3 mg/24 h.
Indication: Symptomatic treatment of mild to moderately severe Alzheimer's dementia.
Dosage: In patients with mild to moderately severe dementia associated with Alzheimer's disease,: Initiation and re-initiation of therapy should start with one Exelon Patch 5 each day. If well tolerated, it may be increased after a minimum of 4 weeks of treatment to one Exelon Patch 10 each day which is the recommended effective dose. Patients treated by Exelon capsules or oral suspension with a maintenance dose of 3 to 6 mg/day may be switched to Exelon Patch 5. A patient on a stable and well tolerated dose of 9 mg/day Exelon capsules or oral suspension can be switched to Exelon Patch 10. If the oral dose of 9 mg/day has not been stable and well tolerated, a switch to Exelon Patch 5 is recommended. A patient on a dose of 12 mg/day Exelon capsules or oral suspension can be switched to Exelon Patch 10. . A minimum of 6 months of treatment and good tolerability with the previous dose should be observed before titrating up to higher doses.
Method of administration: Transdermal patches should be applied once a day to clean, dry, hairless, intact healthy skin on the upper or lower back, upper arm or chest, in a place which will not be rubbed by tight clothing. It is not recommended to apply the transdermal patch to the thigh or to the abdomen due to decreased bioavailability of rivastigmine observed when the transdermal patch is applied to these areas of the body.
The transdermal patch should not be applied to skin that is red, irritated or cut. Reapplication to the exact same skin location within 14 days should be avoided to minimise the potential risk of skin irritation.
Contraindications: Known hypersensitivity to rivastigmine, other carbamate derivatives, or other ingredients of the formulation. Previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine transdermal patch.
Precautions/Warnings: Medication misuse and dosing errors with Exelon transdermal patch (e.g. not removing the old patch when putting on a new one and the use of multiple patches at one time) have resulted in serious adverse reactions; some cases have required hospitalization, and rarely led to death. Patients and their caregivers must be instructed on important administration instructions for Exelon transdermal patch. ♦If treatment is interrupted for longer than three days, treatment should be re-initiated with Exelon Patch 5. Gastrointestinal adverse effects have been observed at initiation of therapy and shortly after dose increase. ♦Caution in case of prolonged vomiting or diarrhoea (risk of dehydration). ♦Extrapyramidal symptoms may be exacerbated by cholinomimetics and worsening of parkinsonian symptoms (particularly tremor) has been observed in patients treated with oral rivastigmine. Adverse effects may respond to removing the patch. If they persist, the daily dose should be temporarily reduced to the previous well-tolerated dose. ♦Patient's weight should be monitored during therapy with Exelon Patch. ♦As with other cholinomimetics, caution is recommended in patients with sick sinus syndrome, conduction defects (sino-atrial block, atrio-ventricular block), gastroduodenal ulcerative conditions, history of or current respiratory disease, urinary obstruction, and seizures in predisposed patients. ♦In case of disseminated skin hypersensitivity reactions with the use of rivastigmine, treatment should be discontinued. Use of rivastigmine patch may lead to allergic contact dermatitis, in this case treatment should be discontinued and patients should be switched to oral rivastigmine only after negative allergy testing and under close medical supervision. Some patients sensitized by exposure to rivastigmine patch may not be able to take rivastigmine in any form. ♦Caution in patients with clinically significant hepatic impairment ♦Caution in patients with body weight below 50 kg: carefully titrate and monitor these patients for adverse reactions (e.g. excessive nausea or vomiting) and consider reducing the dose if such adverse reactions develop. . Exelon should not be used during pregnancy unless clearly necessary. Women on Exelon should not breast-feed.
Interactions: Caution in case of concomitant use with cholinomimetic drugs, anticholinergic medications, succinylcholine-type muscle relaxants during anaesthesia.
Adverse reactions: Very common: **nausea.**
Common: vomiting, anorexia, decreased appetite, anxiety, depression, insomnia, dizziness, headache, diarrhoea, dyspepsia, abdominal pain, urinary incontinence, application site reactions (erythema, pruritus, oedema), fatigue, asthenia, weight decrease, urinary tract infection.
Uncommon: dehydration, agitation, delirium, hallucinations, aggression, cerebrovascular accident, syncope, somnolence, psychomotor hyperactivity, cardiac arrhythmia (e.g. bradycardia, supraventricular extrasystole), gastric ulcers, gastrointestinal haemorrhage, hyperhidrosis, contact dermatitis, malaise.
Rare: hypertension, application site hypersensitivity, pruritus, rash, erythema, urticaria, blister, dermatitis allergic, fall.
Very rare: tachycardia, atrioventricular block, atrial fibrillation, pancreatitis, seizure, worsening of Parkinson's disease.
Not known: restlessness, sick sinus syndrome, hepatitis, abnormal liver function tests, disseminated cutaneous hypersensitivity reactions.
Additional adverse reactions observed with Exelon capsules/oral solution: severe vomiting associated with oesophageal rupture (very rare); angina pectoris, myocardial infarction, duodenal ulcers (rare); tremor, confusion (common).
Packs and prices: Country specific.
Legal classification: Country specific.
Ref : EMA June 2013

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