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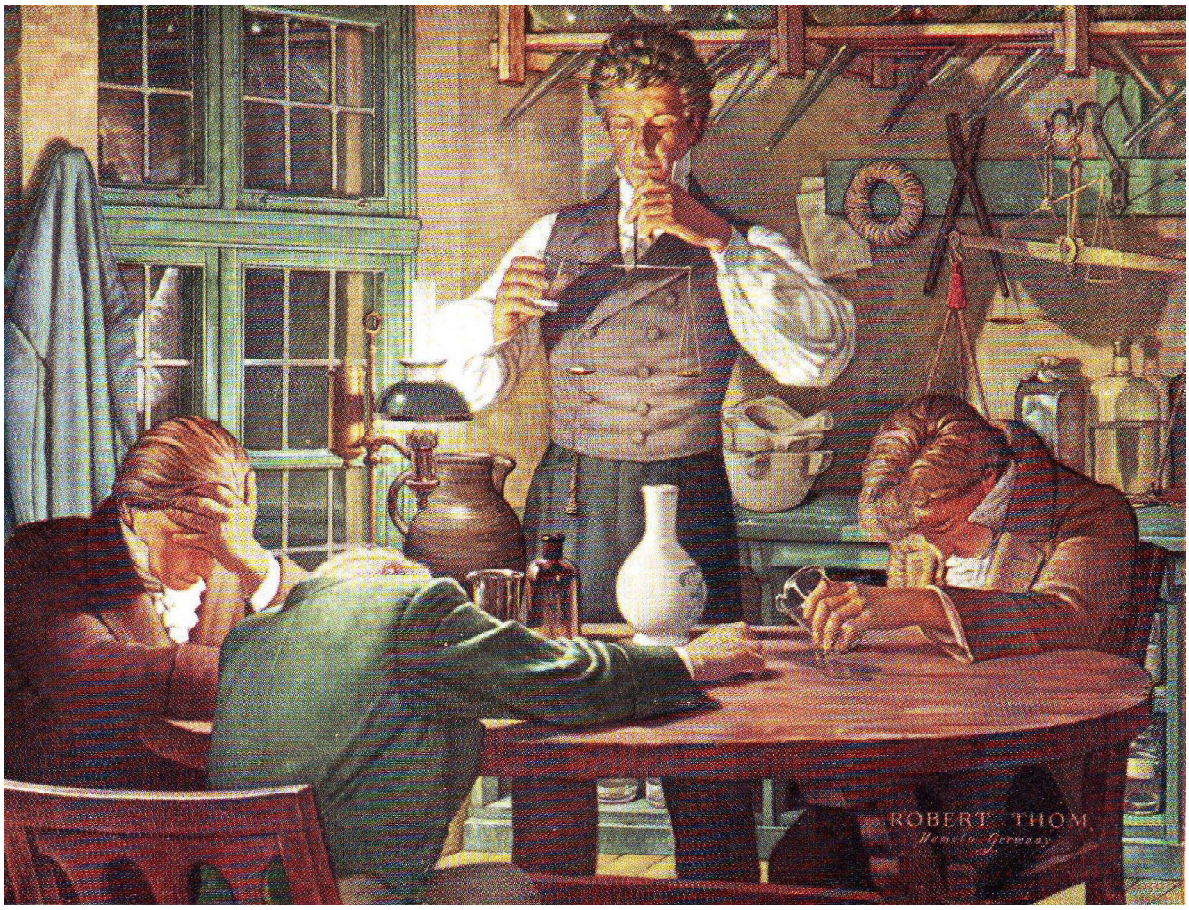

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Cover picture

Sertürner, first alkaloid chemist (About 1816)

Friedrich Wilhelm Sertürner, young German apothecary, discovered plant alkaloids, and isolated morphine from opium. Extensive experiments, including physiologic tests of morphine on himself and three friends, took place in his apothecary shop.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

George A. Bender, Director Robert A. Thom, Artist

Management of febrile seizures

Introduction

Febrile seizure (FS) is the commonest seizure disorder in childhood, affecting 2-5% of all children between the ages of 6 months and 5 years. By definition FSs occur in the context of a febrile illness, not secondary to a central nervous system (CNS) infection or an altered metabolic state, in children who have not had any previous afebrile seizures. There are two main clinical forms. Simple febrile seizure is a single episode of generalised tonic-clonic seizure lasting less than 10-15 minutes, occurring during the first 24 hours of a febrile illness. Complex febrile seizures last longer, or occur after the first 24 hours, or are multiple seizures during the same febrile illness, or convulsions affecting only one side of the body. More than 70% of the FSs are simple febrile seizures.

The aetiology of febrile seizures has been extensively explored. Although the rate of rise in temperature has been implicated there is no definite evidence to support this. FSs may occur even at normal body temperature. Twenty four percent have a family history of febrile seizures, and 4-6% have a family history of epilepsy. The inheritance pattern is mostly polygenic but autosomal dominant inheritance patterns may occur in a few families. Several chromosomal loci and a few genes have been identified. Mutations in the sodium channels and GABA receptors may be responsible for FS. Hence FSs are likely to be convulsions that occur in the context of a febrile illness during a certain window period of the brain's development owing to their genetic potential.

Outcome of febrile seizures

Febrile seizures have a good outcome in the majority. More than two-thirds being simple FS, they last for a short duration. In about 87% they abort spontaneously in less than 10 minutes. The main concerns of parents when they see their child with a febrile seizure are risk of death, effect on the child's learning, risk of long term epilepsy, and risk of having another FS. There are no cases of death reported occurring during a FS. There are many population based studies showing that recurrent FSs, whether simple or complex, do not result in learning difficulties, low IQ, or any decline in school performance. The risk of developing epilepsy later in life is minimal in those with simple FS. At 7 years of age the risk is 1.4%, which is similar to the risk of epilepsy in the general population. However by the age of 25 years it may be slightly higher for those who have had multiple simple FS, first seizure at an early age and have a family history of epilepsy. In those with complex febrile seizures the risk of developing epilepsy is higher. Presence of one complex feature, a neurological deficit, and a family history of epilepsy increases the risk by 10% by 7 years. The presence of all three features of complex FS may increase the risk to 49%.

Although the long term outcomes are good, FSs are associated with a high rate of recurrence. One-third (30%) of all children may have at least one recurrence. In those who have a recurrence, 50% are likely to develop a second recurrence. The risk factors for recurrence of FS are

- positive family history of febrile seizures,
- age less than 18 months at the first febrile seizure,
- FS occurring at a low body temperature and occurring within a short time (<1 hour) from the onset of fever.

Acute management

Majority of FSs are simple, abort spontaneously, and do not need any treatment. But it is vital that the parents do not panic. Instead they should put the child in the recovery position (left lateral), stay near the patient, and call for help. At the time of a FS measures to bring down temperature such as sponging, pouring water over the child or the use of antipyretics rectally are not recommended. If a seizure continues beyond 5 minutes, anticonvulsants such as benzodiazepines (diazepam rectally or midazolam intra-nasally or bucally) can be used to terminate a seizure. Treatment of a seizure lasting more than 5 minutes is important since the longer a seizure lasts the more refractory it becomes to treatment. In those who experience a prolonged FS, there is an increased risk that the next FS also may be a prolonged one. Treating these seizures at home using benzodiazepines in the form of rectal diazepam (0.5 mg/kg) or nasal or buccal midazolam (0.2-0.4mg/kg) is recommended if the parents are competent and confident of administering the medications, if a transport facility is available, and if the patient resides within close proximity to a hospital. If the seizure does not show signs of aborting taking the child to the closest hospital is required.

Routine admission to a hospital after a FS is not required. The parents are advised to seek medical advice from their family physician or local doctor once the child recovers from the seizure and the post-ictal drowsiness

that follows. Some of the indications for directing admission to a hospital are, when meningitis cannot be excluded by history and examination, recovery after the seizure is prolonged, the febrile seizure is complex, there is no recordable fever at the time of the convulsion, and when parents need more support and information.

During the initial evaluation it is important to exclude the possibility of an underlying CNS infection, since seizures may complicate a meningitis in about 13-20%. In children the classical signs of meningeal irritation such as nuchal rigidity, Brudzinski sign and Kernig sign are present in less than 30%. During hospital management the child may require investigations to exclude a CNS infection. Although there is a high threshold for performing lumbar puncture in such children, it should be considered more frequently in children with the following features: children less than 18 months of age, following a prolonged convulsion, presence of focal neurological deficits after the seizure, or use of antibiotics before the onset of seizures.

An important part of management of febrile seizures is parental education, provision of correct information and alleviation of their concerns. Educating parents on the relatively good outcome associated with FS, particularly the simple FS which constitute 70-75% of all cases will alleviate these concerns. Taking time off to explain facts is extremely important to reduce their fears, avoid unnecessary panic and, above all, avoiding a "fever phobia" for febrile illnesses in the future. They should be educated about the possibility of recurrence. Since the degree of fever during an illness is not a risk factor for recurrence, the futility of overzealous temperature control needs to be explained. Use of paracetamol during a febrile illness will be useful only to improve the constitutional symptoms. Overdosing with paracetamol or using NSAIDs unnecessarily, particularly diclofenac sodium suppositories, should be discouraged.

Use of prophylactic anticonvulsants

Since most FSs usually abort spontaneously and carry a good prognosis in a majority, using anticonvulsants is not required. They are no longer routinely recommended, particularly for children with recurrent simple FS, as their potential adverse outcomes outweigh the benefits of preventing a recurrence. Benzodiazepines are the most commonly used anticonvulsants in Sri Lanka for intermittent prophylaxis. About 26 children need to be treated with intermittent diazepam to prevent a single recurrence. Benzodiazepines will also affect the clinician's judgment of an underlying central CNS infection.

Long term anticonvulsants such as phenobarbitone, primidone and sodium valproate have been shown to prevent recurrences, but at the cost of potentially serious adverse effects including life-threatening hepatic encephalopathy with sodium valproate. The clinical guidelines for management of febrile seizures do not recommend routine use of long term prophylaxis, particularly for children with recurrent simple FS.

Summary

Febrile seizures are common. Majority are simple FSs and carry no increased risk of epilepsy in later life, increased risk of death or adverse affects on learning. About 30% of children can have recurrences.

The majority of these seizures spontaneously abort within 5 minutes. The management includes placing in the left lateral position, use of benzodiazepines (rectally, intra-nasally or buccally) for control of prolonged seizures, and exclusion of CNS infection. The other important aspect is parental education. Unnecessary emphasis should not be placed on stringent temperature control. Intermittent or continuous prophylaxis is not recommended, particularly for those with simple FS.

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Management of insomnia

Insomnia is the commonest sleep problem in adults. It can result from any combination of four types of sleep disturbance: difficulty falling asleep, difficulty staying asleep, waking up too early and poor quality of sleep. Between 9% and 18% of the general adult population suffer from clinically significant insomnia.

The DSM-IV diagnostic criteria for primary insomnia consist of a number of sleep complaints, including difficulty initiating or maintaining sleep or non-restorative sleep that lasts for at least a month. Insomnia may cause clinically significant impairment in social, occupational, or other areas of functioning. Insomnia does not occur exclusively during the context of other disorders, including other sleep disorders, or medical disorders, or mental disorders, and is not due to the physiologic effect directly of a substance.

There are a number of risk factors for insomnia: older age, female sex, being divorced, separated or widowed, psychiatric illness, medical conditions, cigarette smoking, alcohol and caffeine consumption, and some prescription drugs.

It is clinically useful to divide insomnia into 2 types, primary and comorbid. In primary insomnia (10%) there are life-long sleep problems with no identifiable cause. In comorbid insomnia (90%) there is an association with medical, psychiatric or other sleep disorders. In the past the term secondary insomnia was used for comorbid insomnia. It was thought that in a patient with a psychiatric or medical illness the insomnia was caused by the disease. Current research shows that this is probably not true. The relationship is bidirectional. This is clinically important. Both the insomnia and the other condition need treatment separately.

Evaluation of insomnia

Evaluation is based mainly on a subjective report by the person and, if possible, the family. A sleep diary is useful. More sophisticated methods such as polysomnography and sleep laboratory studies are not necessary initially. A relevant medical, mental state and physical examination, and laboratory investigations should be done to identify comorbid conditions. Among medical disorders chronic pain is an important cause. Insomnia is particularly associated with psychiatric illness. People with insomnia have high rates of depression and anxiety.

Treatment of insomnia

Behavioural strategies

Firstly it is essential to identify and treat any comorbid conditions. For the insomnia specifically give instructions in good sleep habits (sleep hygiene). Though it might not be a cure in itself it will increase the success of other therapy. People with insomnia over time develop bad sleep habits. The principles of sleep hygiene are listed in panel 1.

Panel 1. Principles of sleep hygiene

- Have a regular sleep and wake time
- Regular exercise (but not late evening)
- Increase exposure to bright sunlight during the day
- Reduce exposure to bright light during the night
- Avoid heavy meals and excessive fluids <3 hours from bedtime
- Improve sleep environment (quiet, dark, cool)
- Avoid alcohol, caffeine and nicotine
- Adopt a relaxing routine before bedtime

Two behavioural strategies for the treatment of insomnia are sleep restriction and stimulus control. Many people with insomnia spend too much time in bed trying to obtain sleep. In sleep restriction the hours in bed are limited to sleep time reported, but not less than 5 hours. Stimulus control restricts the time spent awake in bed. It also attempts to remove negative cognitions, such as thinking, “I will be tossing and turning in bed and will not be able to go to sleep”. Behavioural therapy can be quite effective in treating insomnia but it may not be available or suitable for all patients. The principles of stimulus control are shown in panel 2.

Panel 2. Principles of stimulus control

- If not asleep within a few minutes after getting into bed leave the room.
- Go into another room and do something relaxing such as reading.
- When sleepy try over again.
- Repeat this until sleep comes in less than 15-20 minutes.
- It is important to get up at the same time the next day.
- Keep out of bed during the day.

Pharmacotherapy of insomnia

Two categories of medications are used. Non-specific medicines used in other conditions are also used as hypnotics and specific hypnotics. The non-specific medicine groups are antihistamines, antidepressants and antipsychotics.

Non-specific medicines

Antihistamines

Promethazine and chlorpheniramine are used as over the counter preparations for insomnia. They have the advantage of being cheap, relatively non-toxic and non-addictive even if used for long periods. The disadvantages are the cholinergic side-effects; confusion, urinary retention, dry mouth and blurred vision. The risk of side-effects is greater in the elderly. They are also too mild to be of benefit in severe insomnia but the effect is idiosyncratic and they are worth a trial.

Antidepressants

The common ones used are trazodone, amitriptyline, doxepin and mirtazapine. Most of the time they are used in people already on SSRIs for depression. However, in this instance they are not used for their antidepressant activity. They have specific binding at 5HT2A receptor sites. SSRIs which are 5HT2 agonists make sleep worse, whereas drugs which are 5HT2 antagonists improve sleep. Low dose antidepressants also help sleep due to their H1activity and their muscarinic activity. Not much is known is about the hypnotic dose of these antidepressants. For example, doxepin has been used in a dose of 50 mg to 100 mg, but recent studies show that doses as low as 5 mg are effective.

Antipsychotics

Traditionally, low dose chlorpromazine has been used. The newer antipsychotics olanzapine, risperidone and quetiapine are also effective. They are used because of their activity on the H1 and 5HT2A receptors. There is potential for serious adverse effects such as tardive dyskinesia even in low doses when given for people without a psychotic illness.

Drugs approved for insomnia

They fall into 3 categories: benzodiazepines, non-benzodiazepines and melatonin agonists.

Benzodiazepines

Midazolam, diazepam, clobazam, nitrazepam, clonazepam and lorazepam are the benzodiazepines in popular use in Sri Lanka. Midazolam is an ultra-short acting benzodiazepine with a half-life of 2 hours. It is more suitable for people who have trouble falling asleep rather than those who have trouble staying asleep throughout the night. The risk of dependence is higher in benzodiazepines with short half-lives. Hence the potential for dependence is highest in midazolam. Diazepam, clobazam, nitrazepam and clonazepam all have half-lives longer than 12 hours, and are likely to cause significant daytime sedation and impairment of functioning. On balance, lorazepam in a dose range of 0.5 mg to 2 mg is a suitable benzodiazepine for insomnia. It has an intermediate half-life of 12 hours and has no active metabolites.

Non-benzodiazepines

The non-benzodiazepines or 'Z' hypnotics are zolpidem, zaleplon and zopiclone. Zolpidem is quick acting and ideal for initiating sleep. Zaleplon is similar. Zopiclone has a slower onset but longer duration of action. The commonest adverse effect is dizziness. The differences from benzodiazepines are given below.

- Improved selectivity for the GABA receptor alpha-1 resulting in better safety profile while maintaining sedative effects.
- Fewer non-sedating GABA mediated effects (anticonvulsant, muscle relaxant).
- Shorter half- life with lower risk of daytime sedation.
- Does not interfere with the normal sleep architecture.
- Lower risk of dependence and abuse.
- Low risk for tolerance

Unlike the benzodiazepines, the 'Z' hypnotics do not have implied limitations on their duration of use. This is probably due to the long-term clinical experience with these hypnotics and the clinical trial data documenting continued efficacy and safety for extended periods.

Melatonin agonists

Ramelteon is the only approved drug in this category. It acts on the suprachiasmatic nucleus shutting it off and preventing it sending out an arousal signal. Its effect is through the circadian system affecting the sleep-awake cycle. It is not sedative, has no abuse potential, and is the only sleep agent which is not a controlled substance.

New directions

An important substance in the modulation of sleep and wake cycle is hypocretin. It is absent in patients with narcolepsy. Hypocretin antagonists and H1 and H3 receptor antagonists are being studied for the treatment

of insomnia. It is thought that antagonising the H3 presynaptic autoreceptor will promote greater histamine release.

In summary, insomnia is a common problem. It's prevalent in the general population and more in clinical settings. For many it tends be chronic. In clinical practice, most individuals who have insomnia have it comorbidly with other medical, psychiatric, or sleep disorders. To effectively treat insomnia, it's necessary to include both behavioural as well as pharmacological interventions.

Suggested reading

1. NIH State-of-the-Science Conference Statement on manifestations and management of chronic insomnia in adults. NIH Consensus State Sci Statements 2005; **22**: 1-30.
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I have no conflicts of interest regarding this article.

Lifestyle management of hypertension

Summary

Recently updated Australian guidelines recommend that advice on smoking, nutrition, alcohol use, physical activity and body weight should be part of routine management of hypertension for all patients, regardless of drug therapy. Smoking cessations is recommended to reduce overall cardio-vascular risk. Healthy eating, reducing dietary sodium and alcohol intake, regular physical activity and achieving a healthy body weight are all effective in lowering blood pressure.

Key words: alcohol, cardiovascular disease, diet, physical activity, smoking cessation.

(Aust Prescr 2008,31:150-3)

Introduction

Hypertension is a major risk factor for stroke and coronary heart disease, and is a major contributor to the onset and progression of chronic heart failure and chronic kidney failure. Guidelines by the National Heart Foundation of Australia[1] recommend that doctors caring for patients with hypertension should routinely provide advice on smoking, nutrition, alcohol use, physical activity and body weight.

Lifestyle modification is indicated for all patients with hypertension, regardless of drug therapy, because it may reduce or even abolish the need for anti-hypertensive drugs. In addition to the immediate goal of lowering blood pressure, the recommended lifestyle changes confer a range of health benefits, including better outcomes of common chronic diseases. Effective approaches to promoting lifestyle changes in primary care are listed in Box 1.

Smoking

Smoking is a strong independent risk factor for cardiovascular disease. Quitting is acknowledged to be one of the most effective lifestyle interventions for preventing cardiovascular disease and premature deaths.

Smoking causes an immediate increase in blood pressure and heart rate that persists for more than 15 minutes after one cigarette. People who smoke show higher ambulatory blood pressure levels than non-smokers.[2]

Elevated blood pressure and smoking are the two most important risk factors for subarachnoid haemorrhage in the Asia-Pacific region.The risk of myocardial infarction is 2-6 times higher and the risk of stroke is three times higher in people who smoke, compared with non-smokers.[1]

Smoking cessation markedly reduces overall cardiovascular risk, including the risk of coronary heart disease and stroke, compared with continued smoking. In patients with coronary, heart disease, smoking cessation is associated with a 36% reduction in the risk of all-cause mortality.[3] Although smoking is known to increase the risk of developing hypertension, there is currently no evidence that smoking cessation directly reduces blood pressure in people with hypertension.[2]

Nutrition

Determining the influence of various nutrients on blood pressure and cardiovascular risk is a complex and evolving research area. While some relationships between food and cardiovascular health have not yet been clearly quantified, there is sufficient evidence to recommend that people with hypertension should avoid salty foods and aim for a healthy eating pattern.

Restricting salt intake

High dietary sodium intake is associated with an increased incidence of stroke, and with increased risk of death due to coronary heart disease or cardiovascular disease.[4] Reducing dietary sodium by approximately 1700 mg (75 mmol) per day can lower systolic blood pressure by 4-5 mmHg in hypertensive individuals and 2 mmHg in normotensive individuals.[4,5] This may reduce the need for anti-hypertensive drugs. Responses vary between individuals and are generally greatest among the elderly and those with severe hypertension.

There is weak evidence suggesting that weight loss combined with reduced dietary sodium may be more effective at lowering blood pressure than salt avoidance alone.[4] Reduced-salt diets in combination with thiazide diuretics may predispose elderly patients to hyponatraemia, so electrolytes should be monitored regularly.

Dietary potassium

Some clinical trials suggest that increasing dietary potassium by approximately 2100 mg (54 mmol) per day can reduce systolic blood pressure by 4-8 mmHg in hypertensive individuals and 2 mmHg in normotensive individuals. Potassium-rich whole foods, such as bananas, kiwi fruit, avocado, potatoes (with skin), nuts and yoghurt, are more effective in reducing blood pressure than potassium supplements, which are potentially toxic.[4]

High potassium intake can produce hyperkalaemia in people with impaired renal function. It should be recommended only for those with known normal renal function.

Healthy eating

Blood pressure reductions in people with and without hypertension can be achieved by a healthy eating pattern based on the Dietary Approach to Stop Hypertension (DASH) diet, in addition to reduced salt intake.[4] The DASH diet emphasises fruits, vegetables, whole grains, low-fat dairy products and dietary fibre, while being low in dietary sodium, cholesterol and saturated fat.[6]

High-dose (at least 3 g/day) omega-3 polyunsaturated fatty hypertensive individuals.[2] Evidence is insufficient to recommend calcium and magnesium supplements or increasing dietary fibre intake alone (for example, taking supplemental fibre rather than increasing fruit and vegetable intake) to reduce blood pressure.

Alcohol

Evidence for cardiovascular benefits of light drinking has been challenged by a recent meta-analysis.[2] Regardless of this debate, evidence is emerging that all levels of alcohol intake increase blood pressure. Moderate drinking can increase blood pressure, while binge drinking appears to increase the risk of hypertension.[1] Epidemiological data show a linear relationship between alcohol consumption and hypertension prevalence.[2] Reducing alcohol consumption can lower systolic blood pressure by an average of 3.8 mmHg in patients with hypertension.[7] The Heart Foundation recommends that patients with hypertension limit their alcohol intake to a maximum of two standard drinks per day for men, and one standard drink per day for women[1].

Physical activity

It is clear that physical activity lowers resting and daytime ambulatory blood pressure.[1] In clinical trials of people with hypertension, regular aerobic activity reduced systolic blood pressure by an average of 6.9 mmHg and diastolic blood pressure by 4.9 mmHg.[8]

Box 1

Lifestyle recommendations for lowering blood pressure

Smoking

Give all patients clear, unambiguous advice to stop smoking. Assess for nicotine dependence (e.g. time of last cigarette, withdrawal symptoms) and offer counselling, support services and pharmacotherapy as appropriate.

Nutrition

Advise patients to limit salt intake to 4 g/day (65 mmol/day sodium) or less by choosing foods normally processed without salt, foods labelled 'no added salt' or 'low salt' (or 'reduced salt' products when other options are unavailable). High-salt processed foods (ham, bacon, sausages, canned or packet soups, stock cubes), salty snacks, takeaway foods high in salt, or salt added during cooking or at the table should be avoided.

Advise patients to eat a diet that includes mainly plant-based foods (e.g. fruits, vegetables, pulses and a wide selection of wholegrain foods, moderate amounts of low-fat or reduced-fat dairy products), moderate amounts of lean unprocessed meats, poultry and fish, moderate amounts of polyunsaturated and monounsaturated fats (e.g. olive oil, canola oil, reduced-salt margarines).

Patients with hypertension who are not taking potassium-sparing diuretics and have normal renal function can be advised to increase potassium intake by eating a wide variety of fruits and vegetables, plain unsalted nuts (limit quantity and frequency to avoid excess kitojoules), and legumes (e.g. beans, lentils, dried peas).

Alcohol

Advise patients to limit alcohol intake to a maximum of two standard drinks per day (men) or one standard drink per day (women) and have at least two alcohol-free days per week.

Physical activity

Advise patients to become physically active. Aim for 30 minutes of moderate intensity* physical activity on most, if not all, days of the week.[1] The daily dose can be accumulated in shorter bouts (e.g. three 10-minute walks). Advise against isometric exercise routines that may raise blood pressure (e.g. weightlifting), except within professionally supervised programs.

Body weight

Advise patients with hypertension how to achieve and maintain a healthy body weight targets†: waist circumference less than 94 cm (men) or less than 80 cm (women) and body mass index (BMI) less than 25 kg/m^2.

* 'Moderate' means any activity sufficiently intense to cause a slight increase in breathing and heart rate, and may cause light sweating (e.g. brisk walking, lawn mowing, low-paced swimming, cycling, gentle aerobics).

† Targets are based on data from European populations and may not be appropriate for all ages and ethnocultural groups. Compared with Europeans, the BMI cut-point associated with increased risk of type 2 diabetes and cardiovascular disease is typically higher for Polynesian populations and lower for Aboriginal and Torres Strait Islander populations and some Asian populations.

Regular physical activity has an independent cardio-protective effect.[1] Regular exercise is associated with an increase in high-density lipoprotein cholesterol and with reductions in body weight, waist circumference, percentage body fat, insulin resistance, systemic vascular resistance, plasma noradrenaline and plasma renin activity.[8]

Body weight

There is a direct association between blood pressure and body weight and/or abdominal adiposity. Weight loss studies show that clinically significant blood pressure reductions can be achieved by modest weight loss in people with and without hypertension and that blood pressure reduction is proportional to weight loss.[2] Every 1% reduction in body weight lowers systolic blood pressure by an average of 1 mmHg.[1] Losing 4.5 kg reduces blood pressure or prevents hypertension in a large proportion of overweight people, while losing 10 kg can reduce systolic blood pressure by 6-10 mmHg.[1] In overweight patients with hypertension, weight-reducing diets can achieve a 3-9% decrease in body weight and may reduce systolic and diastolic blood pressure by approximately 3 mmHg.

Weight reduction confers a range of other cardiovascular health benefits including reduced insulin resistance and hyperlipidaemia, and reduced risk of left ventricular hypertrophy and obstructive sleep apnoea.[2]

Integrating lifestyle advice into clinical management

Practical resources are now widely available to help Australian health professionals effectively promote positive lifestyle changes (see Box 2).

Box 2

Resources for promoting lifestyle management to patients

- Heart Foundation's Heart Health Information Service – for professional and consumer resources phone 1300 36 27 87.
- Lifescripts (including resources developed for Aboriginal and Torres Strait Islander people and pregnant women) http://www.agpn.com.au
- Litt J, editor. The 'Green Book'. Putting prevention into practice. 2nd ed. South Melbourne: Royal Australian College of General Practitioners; 2006.
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- Quit resources: http://www.quit.org.au

These encourage and support health professionals to take a systematic approach, by providing a simple framework for broaching the subject with patients, negotiating goals, giving tailored advice including written information, and referring patients to more information and other medical and support services.

The '5As' approach – Ask, Assess, Advise, Assist and Arrange – is often advocated as a useful framework for primary care health professionals to provide brief interventions for lifestyle modification in the clinical setting.

Conclusion

Current Australian guidelines for the management of hypertension recommend lifestyle modification as an important and effective first-line treatment strategy. In addition to the significant lowering of blood pressure achieved through changes to eating patterns, moderating alcohol intake, weight loss and regular physical activity, lifestyle measures (including smoking cessation) confer other significant cardiovascular health benefits. Regardless of other treatments indicated, all patients who need to lower their blood pressure should be given advice and support to achieve and maintain healthy behaviours.

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Management of acne

Acne is a chronic disease of the pilosebaceous unit. It is characterised by the formation of comedones, erythematous papules and pustules, less frequently by nodules or pseudocysts, and sometimes by scarring. Pathogenesis of acne involves increased sebum production, increased *Propionibacterium acnes* proliferation, cornification of the pilosebaceous duct and inflammation.

Classification of acne into mild, moderate and severe is important in selecting treatment modalities. *Mild acne* is characterised by less than 20 comedones, or less than 15 inflammatory papules, or a comedone/papule count of less than 30 on the face. In *moderate acne* the papules and pustules total 15-50, with comedones, and rarely cysts. Total lesion count (comedone, papule and pustule) may range from 30-125 on the face. *Severe acne* denotes the presence of inflammatory nodules and cysts. Also present are comedones, papules and pustules, with a total lesion count greater than 125 on the face.

General principles of treatment

Acne can be effectively treated, although response may be slow. Advise patients to avoid if possible, extremely humid conditions, eg. working in an unventilated kitchen. Review possible contributing factors, such as hormonal (polycystic ovary syndrome), mechanical (hockey masks), and medications (steroids, INAH, rifampicin), and modify these when possible. Try not to apply irritant oils or cosmetics to the affected skin. Abrasive skin treatments can aggravate both comedones and inflammatory lesions. The patient should not scratch or pick the spots. There is no relationship between any particular foods and acne. Women should be informed that acne may worsen during the week before a menstrual period, and all should receive instructions about proper skin care and application of topical medication.

Treatment modalities

There are several treatment modalities that are effective in the treatment of acne. They include,

- retinoids – topical and oral
- antimicrobial therapy – topical and oral
- combination therapy
- hormonal therapy
- adjunctive therapy

Retinoids

Topical retinoids inhibit the formation of microcomedones (precursor lesions), reduce mature comedones and inflammatory lesions, promote normal desquamation of follicular epithelium and may be anti-inflammatory. They may enhance penetration of other drugs, maintain remission of acne by inhibiting microcomedone formation, and prevent new lesions.

Most patients with acne benefit from the use of retinoids. Topical retinoids target the microcomedone and should be used as first-line therapy for mild to moderate inflammatory acne and comedonal acne, except in very severe disease. It is also preferred as maintenance

therapy. Topical retinoids should be the initial treatment for most forms of acne and can be used early for best results. It should be applied to the entire affected area and combined with antimicrobial therapy when inflammatory lesions are present.

Tretinoin 0.025%, 0.05% and 0.1% cream, 0.01 and 0.025% gel, isotretinoin gel and cream, and adapalene gel are available as topical preparations. Isotretinoin causes less irritation than tretinoin, and adapalene is better tolerated than tretinoin.

Oral retinoids are indicated in severe nodular acne and moderate or severe acne unresponsive to topical therapy, moderate to severe acne that affects patients physically and psychologically, inflammatory acne resistant to conventional therapy, and chronic acne that is prone to relapse.

Start treatment with isotretinoin 0.5 mg/kg, and depending on the response increase the dose to 1.0 mg/kg daily. The average duration of treatment is 20 weeks and the total dose should not exceed 120-150 mg/kg weight. Women with facial acne respond better than males with truncal acne. Most patients (85%) respond by 16 weeks, about 10% take 5-6 months to respond, and the rest take a longer period.

Common side-effects of isotretinoin include cheilitis, facial dermatitis, dry skin, nasal dryness, blepharo-conjunctivitis, arthralgia, myalgia and headache. If there is severe headache, decreased night vision or psychiatric events the drug should be withdrawn immediately. Serum lipids should be routinely measured.

Topical antibiotics

Topical antibiotics and benzoyl peroxide are indicated in patients with mild to moderate inflammatory acne, although benzoyl peroxide alone significantly improves inflammatory acne in some patients. Addition of benzoyl peroxide or azaleic acid to a topical antibiotic reduces the development of resistance to *Propionibacterium acne*. Clindamycin or erythromycin are generally used, and should be discontinued once improvement is seen. If no improvement occurs in 6-8 weeks, alternative therapy should be considered.

Benzoyl peroxide is safe and effective. It is available in concentrations ranging from 1% - 10%. Gel forms are preferred to creams, and should be used twice a day to the entire affected area. Side-effects include cutaneous irritation and dryness and bleaching of clothes.

Oral antibiotics

Oral antibiotics are useful in moderate to severe inflammatory acne. Available agents include tetracyclines, macrolides (eg. erythromycin), cotrimoxazole, and trimethoprim. Cephalosporins, fluoroquinolones, aminoglycosides, chloramphenicol and sulphonamides should not be used.

Combination therapy

Topical retinoids plus antimicrobial agents are the mainstay of combination therapy, which is effective in both inflammatory and comedonal lesions. A topical or oral antibiotic in combination with a topical retinoid reduces acne lesions faster.

Hormonal therapy

Hormonal therapy is indicated only in carefully selected cases. They include young women with mild acne who require contraception, as an alternative to repeated course of isotretinoin, in women with severe seborrhoea, androgenic alopecia, seborrhea / acne / hirsutism / alopecia (SAHA) syndrome, and some patients with prepubertal severe acne.

Hormonal therapy consists of antiandrogens (cyproterone acetate, spironolactone, oestrogens) that block ovarian and adrenal androgen production. The goal of hormone therapy is to oppose the effects of androgens on the sebaceous glands and follicular keratinocytes. Appropriate patient selection is extremely important.

Adjunctive therapies

Extracting comedones results in an immediate improvement and topical anaesthesia may be needed for removing closed comedones. Light cautery or laser puncture may be used for removing comedones.

After acne is brought under control, chemical peels are useful in correcting surface scarring and hyperpigmentation. Peeling agents include glycolic acid and trichloroacetic acid.

In patients with mild to moderate acne, use of limited spectrum UV wavelengths have been associated with significant reduction in acne after 4-12 weeks. Prolonged use of ultraviolet may enhance comedogenesis and damage skin.

Treatment of acne during pregnancy

Acne is common during pregnancy. In pregnancy all previous medications should be stopped. Most patients will require nothing more than counselling. Oral

isotretinoin must not be prescribed during pregnancy as it is teratogenic and women must avoid pregnancy for at least four weeks after stopping isotretinoin. Topical benzyl peroxide and erythromycin can be prescribed if drug therapy is essential, on an individual basis. In severe acne during pregnancy oral erythromycin followed by topical benzoyl peroxide may be useful.

The impact of acne on quality of life

Acne has a significant effect on patients' quality of life. Negative effects on social functioning are often greater than that observed with more serious medical conditions such as asthma and epilepsy. Acne may be associated with anxiety, depression, and higher-than-average unemployment rates. The emotional effects of acne are not always easy to assess. Clinically effective treatment of acne can dramatically improve patients quality of life.

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Management of tetanus

Tetanus has been aptly described as a third world disease the treatment of which requires first world technology. Tetanus usually follows recognised injury; in half of the cases the injury is trivial and not considered as serious enough to seek medical advice. The classical triad of rigidity, muscle spasms and autonomic dysfunction are seen in more severe and late presentations. Laboratory investigations are not helpful for confirming of the diagnosis but may be of use in excluding similar conditions.

Pathophysiology

Tetanus is caused by *Clostridium tetani*, a gram positive, spore forming anaerobic bacillus. It is found in manure and soil and enters the body through abraded skin. It multiplies and produces toxins: tetanospasmin and tetanolysin. Tetanospasmin is a potent neurotoxin that leads to the clinical syndrome of tetanus, whereas tetanolysin is capable of locally damaging viable tissue surrounding the infection and optimising the conditions for the bacterial multiplication.

Tetanospasmin is distributed widely via the blood-stream. It is taken up by the neuromuscular junction of the motor neurons and is transported intra-axonally towards the central nervous system. The toxin is then concentrated in the cell body. This retrograde transport first occurs in the motor neurons and then sensory and autonomic neurons. The differential timing of the transportation of the toxin explains the sequence of symptom manifestation.

The symptoms appear only after the toxin has gained access to the presynaptic terminals of the inhibitory cells that release gamma-aminobutyric acid (GABA) and glycine. This blocks inhibition both in the brainstem and the spinal cord, initially causing an increase in resting muscle tone and later in more generalised hyperreflexia and spasms. Rigidity progresses in a descending manner first with dysphagia, risus sardonicus and neck stiffness. Autonomic dysfunction is seen as increased basal sympathetic activity and episodes of sympathetic over-activity resulting tachycardia, arrhythmias, labile hypertension, pyrexia and profuse sweating. In addition,

autonomic storms occur with marked cardiovascular instability. Severe hypertension and tachycardia may alternate with profound hypotension, bradycardia or recurrent cardiac arrest resulting from an autonomic withdrawal.

Tetanus toxin predominantly inhibits acetylcholine release at the neuromuscular junction and it only recovers by new synapses sprouting from the nerve terminal. The toxin binding appears to be irreversible and recovery from the illness occurs because of the re-growth of the axon terminals and by toxin destruction. Disinhibitory effect on the motor neuron overwhelms any diminution of function at the neuromuscular junction.

Unusual forms of presentation are seen with cephalic and local tetanus. Cephalic tetanus presents after wounding of the head and neck, with paralysis of the cranial nerves. Facial paralysis and diplopia are common. The diagnosis may be missed initially but the other symptoms such as trismus, dysphagia and spasms follow rapidly. In local tetanus spasms and rigidity are confined to a local area.

Severity

The severity of tetanus is usually predicted on the basis of the incubation period, the onset time (time from first symptom to first spasm), and the state of immunity. Incubation periods of less than 14 days and onset periods of less then 48 hours are said to herald a severe attack.

The duration of the established illness is fairly constant whatever the grade of severity. Signs become progressively more severe during the first week, reach a plateau during the second week and wane in the third week. Some stiffness may persist for a further 2-3 weeks.

Management

The following are the objectives in the management of tetanus.

1) Eradication of the organism.
2) Neutralisation of the toxin.
3) Symptomatic treatment of the effects of the toxin,
   - muscle spasm
   - autonomic dysfunction
4) Supportive care
   - ventilation
   - Physiotherapy
   - Attention to fluid and electrolyte balance
   - Nutrition
   - Bladder, bowel, skin and oral care
   - Prevention of deep vein thrombosis
   - Psychological support
5) Active immunisation

Eradication of organism

The wound must be cleaned under anaesthesia with wide excision of devitalised tissue. Metronidazole is the antibiotic of choice because of its effective penetration of devitalised tissue, and its activity against anaerobes. Penicillin which was used for many years has now been discarded due to the GABA antagonistic action which further enhances the tetanic spasms.

Neutralisation of the toxin

Neutralisation of the toxin should be undertaken as early as possible since the toxin becomes inaccessible to antitoxin after it enters the central nervous system. Human tetanus immunoglobulin (HTIG) 150 units/kg is considered as the appropriate dose and it should be given i.m. as early as possible.

Control of rigidity and spasms

Spasms and rigidity may lead to compromise of ventilation, exhaustion, aspiration of gastric contents, excessive muscle catabolism, and occasionally ligamental tears or wedge factures of the vertebrae, all of which are life threatening. Hence protection of the airway either by an endotracheal (ET) tube or tracheostomy is mandatory in severe cases. As these patients will have the ET tube in situ for a long period early tracheostomy is preferred.

Sedation

A variety of drugs are used for this purpose namely barbiturates, diazepam, chlorpromazine and morphine. Diazepam, has a GABA agonist action, has established itself because it is an anticonvulsant as well as a muscle relaxant. Diazepam may cause cumulative effects. Intrathecal baclofen, which is also a GABA agonist, has been used to avoid artificial ventilation. Morphine probably acts by replacing the deficiency of endogenous opiates, and tetanus patients tolerate high doses of morphine.

Muscle relaxants

Use of muscle relaxants enables control of muscle spasm. The choice of agent depends on personal preference within the limits of what is available. Muscle relaxants are useful to control intractable spasms during physiotherapy.

Use of magnesium sulphate to control muscle spasms

The role of magnesium sulphate in the treatment was described nearly a century ago. In 1906 Blake described two patients with severe tetanus treated with intrathecal magnesium sulphate. Magnesium is a physiological calcium antagonist. It can be used as the sole agent without the traditional treatment. Its neuromuscular blocking effect is mainly due to competition with calcium for membrane channels on the pre-synaptic terminals. This produces a dose dependent pre-synaptic inhibition of neurotransmitter release in the peripheral nervous system and also blocks catecholamine release from nerve and the adrenal medulla. It also reduces receptor responsiveness to released catecholamine and is an anticonvulsant and a vasodilator.

Monitoring clinical variables such as the patella tendon reflex, respiratory rate, QRS complex and PR interval of the ECG, urine output and measurement of serum magnesium level are essential when using magnesium sulphate therapy. The therapeutic level of serum magnesium is 2-5 mmol/l.

Control of autonomic dysfunction

Autonomic dysfunction in severe tetanus is caused by the effect of tetanosplasmin on brainstem and autonomic neurons and starts a few days after muscle spasms. Autonomic dysfunction is the most dangerous complication of tetanus, and results from increase in basal sympathetic activity and intermittent sudden massive outpouring of catecholamines leading to autonomic storms. During these episodes blood noradrenaline and adrenaline may rise to 10 times basal levels. Episodes of sympathetic overactivity with fluctuating tachycardia, labile hypertension, sweating and pyrexia may be seen. Parasympathetic overactivity may result in profuse salivation and bronchial secretions. This is thought to be due inducing lesions in the vagal nuclei.

Ventilatory and airway support

Aspiration pneumonia and hypoxia are two major complications of tetanus. These can be avoided by early intubation followed soon after by tracheostomy. Early tracheostomy helps to isolate the trachea and facilitates ventilation without undue stimulation of the upper airway. A tracheostomy will also facilitate effective bronchial toilet and mouth care. Tracheostomy is better tolerated by patients for a longer period, and less sedation is required than an endotracheal tube.

Active immunisation

The disease does not confer any significant immunity, and all patients should be actively immunised. The first dose of vaccine should be given as soon as tetanus is suspected. The second dose is usually given one month later. Patients must be requested to come for the third dose in a 6-month follow up.

Complications

Complications may occur as a result of the disease itself or as a consequence of treatment. Asphyxia leading to hypoxia and cardiac arrest, aspiration pneumonia, cardiac failure, pulmonary oedema, arrhythmias, wedge fractures of vertebrae and hyperpyrexia are some of the life threatening complications of the disease itself. Pneumonia and other nosocomial infections, fluid, electrolyte and acid-base imbalances, stress ulceration, sepsis, deep vein thrombosis and embolic phenomena, prolonged ileus and bed sores are some of the complications arising during the course of management.

Conclusion

Tetanus is an easily preventable disease. Therefore effective and active immunisation programs with more public awareness via mass media will greatly reduce the incidence of tetanus. Intensive care of a patient with tetanus is enormously costly.

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Current information about drug registration

New chemical entities registered

Generic name	**Brand name**	**Dosage form**	**Manufacturer**	**Importer**	**Therapeutic class / use(s)**
Aceclofenac	Zerodol	Tablet, 100 mg	IPCA, India	Emar Pharma	NSAID
Moxifloxacin	Moxiget	Tablet, 400 mg	Getz, Pakisatan	Hemas	Quinolone
Telmisartan	Telsart 20	Tablet, 20 mg	Atoz, India	Euro Asian	Antigiotensin – II receptor antagonist

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