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1993 25 YEARS 2018

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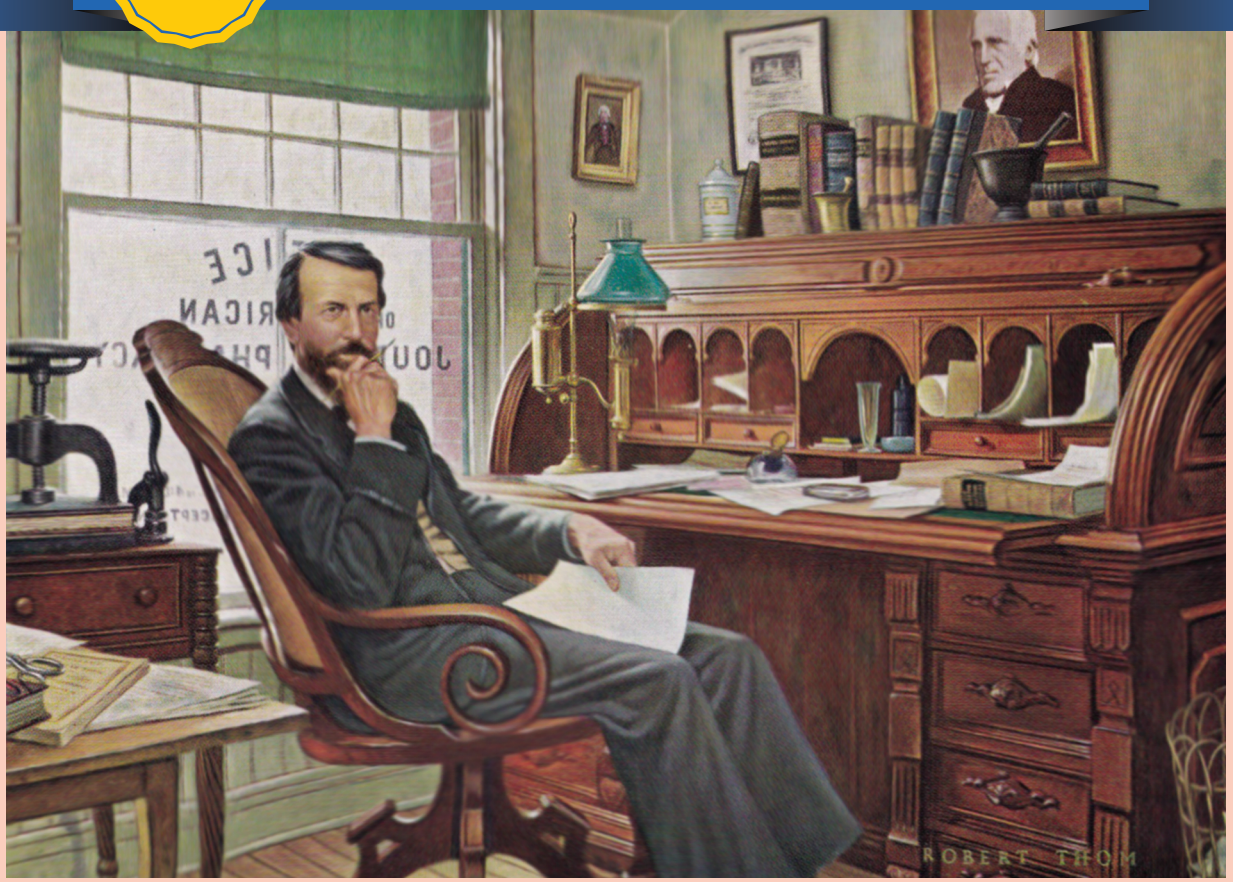

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The Sri Lanka Prescriber

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Cover picture

FATHER OF AMERICAN PHARMACY – WILLIAM PROCTER, Jr. (1817-1874)

William Procter, jr., operated a pharmacy; taught 20 years at Philadelphia College of Pharmacy; helped found the American Pharmaceutical Association; served the U.S.P. for 30 years; edited the *American Journal of Pharmacy*; literally died "in the harness."

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

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

The Sri Lanka Prescriber celebrates 25 years of publication

The Sri Lanka Prescriber which celebrates 25 years of continuous publication in 2018, is Sri Lanka's only national independent drugs and therapeutics information bulletin. It is published quarterly by the Department of Pharmacology, Faculty of Medicine, University of Colombo and the State Pharmaceutical Corporation (SPC) of Sri Lanka. The primary purpose of the bulletin is to help health professionals in Sri Lanka make informed decisions when prescribing, by providing them with independent and reliable information about drugs and therapeutics.

The Sri Lanka Prescriber commenced publication in the present format in 1993 and 2018 marks the 25th year of continued publication. *The Sri Lanka Prescriber* evolved from the pocket size bulletin, '*The Prescriber*' which began publishing in 1973 but went out of print in 1980's. Prior to that '*Formulary Notes*', was in existence from 1966 which was the first drug information bulletin published in Sri Lanka. *Formulary Notes* was also a pocket size bulletin, published on behalf of the Formulary Committee, initiated by Professor Senaka Bibile, the first Professor of Pharmacology, University of Ceylon and the Editor of *Formulary Notes*, to provide unbiased drug information to healthcare professionals. As the *Formulary Notes* had difficulties in publication, '*The Prescriber*' was launched in 1973 as a joint publication between the Formulary Committee and the State Pharmaceuticals Corporation (SPC), with funding and distribution managed by the SPC. *The Sri Lanka Prescriber* commenced as a joint publication by the Department of Pharmacology, Faculty of Medicine, University of Colombo and the SPC in 1993.

The Sri Lanka Prescriber became a full-member of the International Society of Drug Bulletins (ISDB) since 2001. In accordance with ISDB policy the Sri Lanka Prescriber does not accept advertising or other forms of sponsorship. This enables the bulletin to be wholly independent of the industry and other regulatory authorities, allowing it to publish freely and impartially on all matters related to medicines. The SPC bears the publication costs but does not influence contents of the bulletin, which are decided by the editorial board.

The print copy of The Sri Lanka Prescriber has a circulation of 7000, distributed free of charge to Sri Lankan healthcare professionals, including prescribing doctors, academics, researchers and students in universities, not only in medicine and dentistry but also in pharmacy. The bulletin has been made available online via websites of the SPC and the Department of Pharmacology Colombo since 2007.

For well over two decades, the bulletin has provided accurate, independent evaluations and practical advice on drugs and therapeutics for doctors, pharmacists and other healthcare professionals. The Editorial Board of the Sri Lanka Prescriber consists of experts from a variety of disciplines, including pharmacology, clinical medicine, paediatrics, gynaecology and obstetrics, psychiatry, anaesthesiology and dentistry. Surveys of our readership have consistently shown that readers find the bulletin influential in relation to their decisions, recommendations or advice on treatments, becoming an indispensable part of evidence based clinical practice in Sri Lanka. The Sri Lanka Prescriber is funded by the State Pharmaceuticals Corporation (SPC) of Sri Lanka as a service to the medical profession.

Editorial Board, The Sri Lanka Prescriber

Management of glaucoma

Introduction

Glaucoma is a progressive optic neuropathy with characteristic changes in the optic nerve head and corresponding loss of visual field, that is associated frequently but not invariably with a raised intraocular pressure (IOP). It is the second commonest cause of blindness in the world.

The global prevalence of glaucoma for a population aged 40-80 years is 3.54%; ie. an estimate of 64.3 million with glaucoma in 2013, increasing to 76.0 million in 2020 and 111.8 million in 2040 worldwide [1]. Glaucoma is the silent thief of sight where undetected and untreated patients end up in blindness.

Glaucoma encompasses many different sub-types which have varied symptoms, pathophysiology and treatment options. Knowledge of aqueous humour dynamics is of paramount importance in understanding and managing glaucoma. The aqueous humour secreted by ciliary processes into the posterior chamber, flows into the anterior chamber through the pupil. Aqueous humour exits from the eye via two main pathways. Conventionally most of the aqueous is thought to leave through the trabecular meshwork at the irido-corneal angle via the Schlemm canal to drain into the episcleral venous plexus. Any non-trabecular outflow involving passage of aqueous through ciliary muscle and sclera is termed uveo-scleral outflow. The balance of synthesis and drainage maintains the intraocular pressure within the normal range (12-21 mm Hg). In most individuals with glaucoma the optic nerve and visual field changes seen are determined by both the level of IOP and the resistance of the optic nerve to damage [2].

As glaucoma is a heterogeneous group of disorders symptoms depend on the sub-type of glaucoma. In acute glaucoma the main symptom is ocular pain. In chronic glaucoma e.g. primary open angle glaucoma, most of the patients are symptomless.

In primary open angle glaucoma (POAG) the resistance to aqueous outflow is thought to be in the trabecular meshwork. Conversely, in acute angle closure glaucoma the primary pathology is proximal to the meshwork. In acute angle closure there is apposition of peripheral iris to the trabecular meshwork causing the irido-corneal angle to "close". Pupillary block is the most frequent cause of angle closure where flow of aqueous from posterior chamber to anterior chamber through the pupil is impeded at the lens iris interface. This results in a pressure gradient between the two chambers causing peripheral iris to bow forward against the trabecular meshwork [3] obstructing the drainage of aqueous. Traditionally, secondary glaucoma denotes an external mechanism such as trauma, tumours, cataractous lens, inflammatory cells, membranes or developmental abnormality etc. playing a part in impeding the outflow.

Symptoms and signs of Glaucoma

Primary open angle glaucoma is a sub-type that occurs more commonly in the elderly. It is characterized by increase in intraocular pressure (IOP > 21mmHg), an open drainage angle, glaucomatous optic nerve head damage and visual field loss. The risk factors include increasing age, positive family history and myopia.

Another sub-type seen in Sri Lanka is the normotensive (normal tension) glaucoma (NTG) where the eye pressure is within normal limits but with progressive optic nerve damage and visual field defects. Ocular hypertension (OHT) is the sub-type where the IOP increases in the absence of identifiable optic nerve damage or visual field loss. POAG and elevated NTG are asymptomatic until a significant part of the visual field is lost and the presentation is often late.

In contrast acute angle closure glaucoma mostly occurring in elderly females has a dramatic presentation with acute signs and symptoms.

Starting with ocular pain, headache, blurring of vision and sometimes with visualization of halos it may rapidly progress to severe ocular pain, marked redness, photophobia and loss of vision. Sometimes the patient has severe headache, abdominal pain and vomiting so that the patient may end up being admitted to a medical or surgical ward.

This condition, if not detected and treated immediately, the acute IOP rise will lead to permanent optic nerve damage and irreversible blindness.

Diagnosis of Glaucoma

Since glaucoma is mostly a symptomless disease in the initial stages, eye examination and screening is important for early detection. In the assessment of the patient several investigations are utilized. Measuring the intraocular pressure (IOP), evaluating the irido-corneal angle (Gonioscopy), visual field assessment (HVF), and assessing the optic nerve head (OCT) are some of them.

Predisposing causes of Glaucoma

Genetic factors, congenital defects, positive family history, previous eye trauma, ocular inflammation, cataract, long

term uncontrolled diabetes and the use of steroid medications may be associated with glaucoma. For these patients regular screening for glaucoma is important.

Treatment options for Glaucoma

In current practice the main aim of treatment is to minimize the progressive optic nerve damage by reducing the intraocular pressure. Treatment depends on the sub-type and the options include topical, oral, and intravenous medications, laser treatment and surgery. In the management of patients with a diagnosis of glaucoma, factors such as type and stage of the disease, rate of progression and life expectancy of the patient are important considerations. Many clinicians would consider a target pressure based on above factors to prevent further damage to the optic nerve. However this objective should be achieved with the least disruption to patients' daily life. Hence not only adverse effects, interactions and dosage regimes but also the cost of the medications should be taken into consideration in selecting optimum treatment options.

Ocular hypotensive agents are classified into several groups according to the chemical composition and pharmacologic action. The groups of agents in common clinical practice include: 1. Cholinergics (acetylcholine receptor agonists) 2. Carbonic anhydrase inhibitors (CAIs), 3. β-adrenoceptor antagonists 4. Prostaglandin analogues (PGAs) 5. Adrenoceptor agonists and 6. Hyperosmotic agents [2].

Table 1. Glaucoma medications

Medication Class/ Compound	*Mode of Action*	*Dosage forms and regimes*	*Side effects*	*Comments*
Cholinergics (miotics) (anticholine esterases) – Pilocarpine	Increase trabecular outflow	Topical 2-3 times	Miosis, brow ache, increased salivation/ secretions, abdominal cramps	Exacerbation of cataract effect
Carbonic anhydrase inhibitors – Acetazolamide	Decrease aqueous production	Oral/ topical 2-4 times	Depression, malaise, paresthesiae, diarrhoea, acidosis, hypokalemia, renal stones, bone marrow depression, blood dyscrasias	May cause allergy in patients with allergy to sulfa drugs
β-adrenoceptor antagonists (β blockers) – Timolol	Decrease aqueous production	Topical 1-2 times	Blurring, irritation, corneal anaesthesia, bradycardia, heart block, bronchospasm	Potentially dangerous in patients with a history of bronchial asthma
Prostaglandin analogues (PGA) Latanoprost Travoprost Bimatoprost	Increase uveoscleral outflow	Topical Once a day (night time)	Redness, blurring, hyperpigmentation of iris and lids	
α_2 adrenoceptor agonists – Brimoniine	Decrease aqueous production	Topical 2-3 times	Irritation, blurring, lid retraction, headache, fatigue, insomnia, hypotension	May have a neuro-protective effect
Hyperosmotic agents – Mannitol	Creates osmotic gradient; dehydrates vitreous	Intravenous	Headache, nausea, vomiting, renal failure	Contraindicated in renal failure, caution in cardiac failure

Treatment typically begins with the selection of an agent for IOP reduction. Although β-adrenoceptor antagonists are still commonly used by many clinicians, especially in the low resource settings, the PGAs are playing an increasingly important role in the first-line therapy of glaucoma.

Adjunctive agents, such as α-adrenoceptor agonists and CAIs are often effective at providing additional reduction in IOP for patients not controlled on monotherapy. As with any chronic disease, effective treatment depends on minimizing the adverse effects of therapy and maximizing patient compliance.

The introduction of a variety of well tolerated and potent medications over the past few years has allowed the clinician to choose a treatment regimen on an individual patient basis resulting in safe and efficacious therapy in glaucoma. Many of the known systemic adverse effects are rarely encountered in topical therapy, and long term treatment is thus possible as in the case of introduction of topical carbonic anhydrase inhibitors. Redness in the eye and darkening around the eyes are known effects of prostaglandin analogues. β blockers (eg.timolol) should not be prescribed to patients with a history of bronchial asthma. The side-effects of β blockers can be minimized by using selective β blockers such as Levobunolol 0.25%. However, α_2 adrenoceptor agonists should be used with caution in the elderly due to its potential systemic hypotensive effect.

Combined therapy as a single vial has enhanced compliance while reducing the toxic effects of preservatives at the same time. There are different regimes of administration of glaucoma medications ranging from once a day administration to 4 times a day. Use of gel form eg; timolol can reduce the frequency of administration. As glaucoma medications should be continued long-term the patient should fully understand the importance of the continuous treatment.

As the patient does not feel improvement or worsening, it is important to monitor the disease with regular eye pressure checking and visual field assessment. The patient should be involved in understanding and interpreting the investigations. Informed decisions should be taken involving the patient in continuing treatment. Other treatment options in glaucoma management include laser treatment and surgery in selected cases. Alternative strategies that include neuroprotectants are also being investigated at present [3].

Before concluding that a medication is ineffective it is important to check for the correct technique of instillation of eye drops. The correct way of instillation of eye drops is to place one drop in the lower fornix of each eye. Instilling more than one drop is a waste as the conjunctival sac is only capable of holding up to 30 microlitres [4]. Leaking out drops may cause unwanted side-effects such as pigmentation of peri-orbital skin in the case of prostaglandin analogues. When there is more than one type of topical medications, a gap of at least 10 minutes should be allowed between the two types for absorption of the first and to avoid washing off of the first medication by the one that follows. Applying pressure with the index finger over the naso-lacrimal duct at the medial angle of the eye is known to reduce systemic absorption thereby reducing systemic side-effects.

Glaucoma and progressive optic neuropathy with characteristic changes in the optic nerve head and corresponding visual field defects is the second commonest cause of blindness in the world. It is composed of a heterogeneous group of disorders. In current practice the main aim of treatment is to minimize the progressive optic nerve damage by reducing the intraocular pressure. Adverse effects, interactions, dosage regimes and the treatment cost of the medications should also be considered in selecting the optimum treatment option. However, this objective should be achieved with the least disruption to patients' daily life. In current clinical practice many patients achieve good control with advanced medical therapy. When IOP cannot be reduced sufficiently with pharmacological treatment to prevent the risk of progression further treatment options should be considered [5].

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Management of acute ST-segment elevation myocardial infarction

Introduction

Acute ST-segment Elevation Myocardial Infarction [STEMI] is a leading cause of morbidity and mortality worldwide with an annual incidence of approximately 50 per 100,000 in Europe and America [1, 2]. In these countries the in-hospital mortality rates have decreased due to improvements in treatment, and presently vary around 4-12% [1, 2]. Over the years preferred treatment strategy for STEMI has shifted from thrombolysis to primary percutaneous coronary intervention (PCI). In England 98% of approximately 20,000 new STEMI patients received primary PCI in 2014 [3].

In Sri Lanka (SL) the first cross sectional clinical audit of acute coronary syndrome patients in government hospitals covering the entire country done in 2015 showed a country wide in-hospital mortality of 4% in the STEMI group [4, 5]. Only 5.7 % STEMI patients received primary PCI while 63% received fibrinolysis [4, 5]. Extrapolated from the Ministry of Health annual fibrinolytic requirement of approximately 13000 vials, in Sri Lanka an estimated 20,000 acute STEMI patients may present to government hospitals annually. This article describes the current trends in therapeutic management of acute STEMI according to recent evidence based guidelines [1, 2, 6, 7].

Fourth universal definition of myocardial infarction 2018

For epidemiology and research purposes the fourth Universal Definition of Myocardial Infarction (UDMI) is useful [8]. UDMI defines myocardial infarction (MI) pathologically as myocardial cell death due to prolonged ischemia. MI is categorized into five types with differing etiology and prognostic implications according to raised level of the cardiac biomarker troponin (Tn) and additional stipulated electrocardiographic (ECG) or imaging criteria (Table 1). The term 'myocardial injury' is used for cardiac Tn rise without ECG or imaging criteria.

Clinical diagnosis of AMI

Clinically, STEMI is diagnosed in a patient with acute cardiac type chest pain and typical ST segment elevation in the ECG. Rise of Tn and left ventricle (LV) wall motion changes by echocardiogram are optional supportive evidence and are not essential to start the acute STEMI management revascularization protocol.

When ST segment depression or T wave inversion is seen with cardiac type chest pain, a diagnosis of non-ST elevation myocardial infarction (NSTEMI) is made when Tn is raised, while unstable angina (UA) is diagnosed when Tn is normal. UA and NSTEMI are managed with dual anti platelet therapy (DAPT), anticoagulation with low molecular weight heparin enoxaparin, statins and Primary Coronary Intervention (PCI) when indicated according to NSTEMI and UA management protocols [9] which are not discussed here.

Evidence based management of acute STEMI

Acute STEMI is a medical emergency that needs timely diagnosis and treatment. Acute STEMI management guidelines are published by reputed international cardiac societies incorporating latest clinical evidence and adherence to these will improve clinical outcome for patients [1, 2, 7]. In SL the Ceylon College of Physicians published STEMI guidelines incorporating international guidelines with some additional recommendations suited for the local setting [6].

Immediate management of STEMI

- Cardiac monitoring in intensive care with standby defibrillator is recommended for all STEMI patients.
- Intravenous (IV) cannula for emergency IV medications, nasal oxygen in hypoxic patients with arterial oxygen saturation SaO2 <90%, and morphine 2.5 mg IV or a titrated nitrate infusion for severe angina can be started.

Table 1. 4th Universal definition of myocardial infarction – different types of MI

MI type	*Aetiology*	*Tn value*	*Additional criteria*
1	Athero-thrombosis with atheromatous plaque disruption	>99th percentile of normal ECG, imaging	ECG, imaging
2	Oxygen demand supply imbalance	>99th percentile of normal	ECG, imaging
3	Cardiac type death	-	ECG, autopsy
4a	Percutaneous coronary intervention related	>05 times normal	ECG, imaging
5	Coronary Artery bypass grafting related	>10 times normal	

- As soon as possible and in the absence of contra-indications following drugs are recommended
  - Loading dose of non-enteric coated aspirin 300 mg, preferably chewed and swallowed.
  - Loading dose of a platelet P2Y12 inhibitor clopidogrel or ticagrelor depending on the reperfusion strategy planned as described below.
  - High intensity statin therapy such as atorvastatin 40-80 mg.
  - A proton pump inhibitor (PPI) such as panto-prazole 40 mg orally to prevent gastric irritation due to DAP T is reasonable.
- A reperfusion strategy is initiated depending on clinical circumstances and availability of facilities.

A. Reperfusion strategy

The primary aim in acute STEMI is early reperfusion of the infarct related coronary artery (IRA) occluded by the athero-thrombus. A delay in reperfusion leads to loss of myocardium resulting in worsening LV function and poor prognosis.

The best strategy for any given patient is decided on factors such as the time since onset of chest pain, time delay from STEMI diagnosis to primary PCI, clinical condition of patient and bleeding risk. Recommendations for reperfusion strategy in the IRA are given in Table 2.

1. Primary PCI

Primary PCI (PPCI) is the revascularization method of choice unless the anticipated time from STEMI diagnosis to PCI mediated reperfusion is >120 minutes. STEMI patients presenting within 12 hours from start of chest pain, and even those admitted after12-48 hours with clinical or ECG evidence of ongoing ischemia or in cardiogenic shock are also candidates for PPCI. Patients admitted to hospitals without PCI facilities should be transferred urgently in an ambulance with cardiac monitoring, defibrillator facility and an attending doctor, if PCI can be done in <120 minutes, after contacting the emergency PCI team at the hospital. For such transfers a door-in door-out time < 30 minutes at the transferring hospital should be achieved. A patient admitted to a PPCI capable hospital should undergo PPCI within 90 minutes.

Adjunctive treatment for PPCI

- The loading dose of clopidogrel is 600 mg orally is added to initially given aspirin 300 mg. Ticagrelor has shown superiority in clinical outcomes to clopidogrel in the setting of PPCI and is the preferred P2Y12 inhibitor. If available and affordable, loading dose of ticagrelor 180 mg orally is given instead of clopidogrel for PPCI patients.
- At the beginning of PCI an IV bolus of unfractionated heparin (UFH) 70-100 units /kg is given to maintain an activated clotting time of approximately 300 seconds. It is reasonable to give part of this dose (Eg. UFH 4000 units IV bolus) earlier at the ETU or at the transferring hospital in the SL setting if advised by the PPCI team especially when radial access for PPCI is planned.
- Platelet glycoprotein IIb/IIIa receptor inhibitors such as abciximab are used intracoronary at the time of PCI for a large thrombus burden. IV heparin dose at time of PCI needs to be reduced if abciximab is planned.

Routine radial access and drug-eluting stent implant is the standard of care. PPCI to the IRA usually results in immediate reperfusion.

2. Fibrinolytics

When delay for PPCI exceeds 120 minutes from STEMI diagnosis, there is no survival advantage of primary PCI over fibrinolysis. When PPCI is not an option and in the absence of contraindications, fibrinolysis should be initiated immediately ideally <10 minutes of STEMI diagnosis and with a door to needle time <30 minutes. STEMI patients are considered for thrombolysis if presenting within12 hours of initial chest pain and rarely even after 12-24 hours if clinical or ECG evidence of ongoing ischemia is present. Contraindications for fibrinolytics given in Table 3 needs exclusion.

Fibrinolytics available in SL are Tenecteplase (TNK-tPA), Streptokinase (SK) and Alteplase (tPA).

- **Tenecteplase (TNK-tPA)** is the preferred fibrin specific thrombolytic with better reperfusion rates than SK. TNK is now available in most Teaching and Provincial hospitals in SL. It is given as a single IV bolus according to body weight calculated from a dosing chart (Table 4). In some developed countries TNK IV bolus is given by the ambulance team as pre-hospital fibrinolysis, minimizing delays when decided by the hospital emergency cardiac team after telemetric ECG review.
- **Streptokinase (SK)** 1.5 million units IV infusion over 60 minutes is a less expensive alternative but with lesser reperfusion efficacy as it is not fibrin specific. It needs to be started in-hospital preferably in the intensive care unit (ICU) setting with resuscitation facilities while monitoring for allergic reactions, hypotension and arrhythmias. Hydrocortisone 100 mg IV and chlorpheniramine 10 mg IV are usually given prior to starting SK infusion in the ICU setting in most SL hospitals. Previous treatment with SK is a contra-indication for its use.
- **Alteplase (tPA)** 15 mg IV bolus followed by IV infusion given over 90 minutes according to body weight is another alternative thrombolytic. It is more expensive than TNK and carries higher reperfusion rates as well as higher bleeding risks.

Table 2. Reperfusion strategies in the infarct related artery according to time from symptoms onset

Time from symptom onset	Recommended reperfusion strategy
Early presenters <3 h	PPCI is strategy of choice. Fibrinolysis if >120 min delay for PPCI
After 3 up to 12 h	Later the presentation, PPCI strategy better than fibrinolysis
Evolved STEMI 12-48 h	PPCI strategy for all
Recent STEMI >48 h	Angiography and PCI but no PCI to totally occluded IRA after 48 h
At any time	PPCI strategy if clinical, hemodynamic or electrical instability

PPCI – Primary percutaneous coronary intervention, IRA – infarct related artery

Table 3. Contraindications for fibrinolytics

Absolute
Intracranial hemorrhage or stroke of unknown origin anytime
Ischemic stroke within past 6 months
Central nervous system damage, neoplasm or arteriovenous malformations
Major trauma, head injury, surgery within past 6 months
Gastrointestinal bleeding within 1 month
Known bleeding disorders excluding menses
Aortic dissection
Non compressible punctures within past 24 hours [eg.lumbar puncture, liver biopsy]
Relative
Transient ischemic attack in past 6 months
Oral anticoagulant therapy
Pregnancy or within 1 week postpartum
Severe hypertension systolic BP>180 and or diastolic BP>110
Advanced liver disease
Active peptic ulcer
Infective endocarditis
Prolonged or traumatic resuscitation

BP – blood pressure

Table 4. Dosing chart for Tenecteplase [TNK] single IV bolus

30 mg if < 60 kg
35 mg if 60 to < 70 kg
40 mg if 70 to < 80 kg
45 mg if 80 to < 90 kg
50 mg if 90 kg or more
Half dose if age 75 years or more

Adjunctive treatment for fibrinolytics

- The loading dose of clopidogrel is 300 mg orally is added to initial dose of aspirin 300 mg.
  Ticagrelor has not been studied as adjunctive treatment for fibrinolytics.
- If age < 75 years, enoxaparin 30 mg IV bolus is given followed by subcutaneous (SC) injection 15 min later at 1 mg per kg up to a maximum of 100 mg per injection every 12 hours. Enoxaparin is continued until PCI or minimum 48 hours to a maximum of 8 days or until hospital discharge.
- If > 75 years, enoxaparin IV is not given. Enoxaparin is started with SC dose of 0.75 mg per kg, up to maximum of 75 mg per injection given 12 hourly. SC dose is given once daily in renal failure.

3. Pharmaco-invasive strategy

For this option, following initial fibrinolysis and successful reperfusion, patient is routinely transferred for PCI to be performed within 3-10 hours. This strategy is especially useful in the SL setting for hospitals with transport delays > 120 min to reach a PPCI capable hospital. This strategy is especially successful for low bleeding risk patients who present early within < 2 to 3 hours of chest pain onset. Routine PCI after fibrinolysis may improve outcomes by preventing re-infarction associated deaths.

In failed reperfusion indicated by clinical deterioration and ST segment resolution < 50% at 90 min from fibrinolytic initiation, the patient should be immediately transferred for rescue PCI. Rescue PCI has shown better outcome than repeat fibrinolysis or conservative management in this category of patients.

Adjunctive treatment for pharmaco-invasive strategy

- Adjunctive treatment is similar to that given with fibrinolytics.
- At PCI, Heparin IV dose may need reduction due to prior fibrinolytic and enoxaparin use and GPIIb/IIIa inhibitors are best avoided to minimize bleeding complications.

B. Late (>12 hours) presentation of STEMI

Supportive medications are similar to adjunctive treatment for fibrinolysis. Fibrinolysis is not indicated in this group.

- Regardless of the time from symptoms onset, ongoing ischemia, hemodynamic instability, or life threatening arrhythmia is an indication for a primary PCI strategy [1].
- Evolved STEMI (12-48 hours) and recent STEMI (>48 hours) are also recommended a Primary PCI strategy but a completely occluded IRA is not opened after 48 hours [1].
- After 48 hours in stable patients, non-invasive tests for residual ischemia or viability are done to decide whether a late invasive strategy or elective coronary angiography should be done.

C. Secondary prevention medications

Following drugs have proven survival benefit in AMI. In the absence of contraindications these are started within 24 hours and continued at hospital discharge and long term.

- **Low dose aspirin** 75-150 mg nocte is recommended for life.
- **P2Y12 inhibitor**
  - **Clopidogrel** – As part of DAPT with aspirin, clopidogrel 75 mg orally daily is recommended for minimum 1 year and can be extended at the discretion of the treating physician.
  - **Ticagrelor** – For PPCI patients who received a loading dose, maintenance dose of ticagrelor is 90 mg orally twice daily [BD] for one year and 60 mg BD if continued after one year up to 3 years.
    Aspirin dose should be <100 mg when ticagrelor is used.
    Ticagrelor is not suitable if body weight <60 kg and for triple therapy with warfarin.
- **Statin** – high intensity atorvastatin 40-80 mg to achieve fasting low density cholesterol (LDL) <70 mg/dl. Statins act in plaque stabilization.
- **Beta blockers (BB)** – carvedilol, bisoprolol, metoprolol or nebivolol are useful in all patients and particularly if left ventricular ejection fraction (LVEF) <40%. Atenolol can be given if no LV dysfunction. BB reduce risk of ventricular fibrillation after AMI.
- **Angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker [ARB]** should be started within 24 hours in all AMI patients and particularly in patients with LVEF < 40%, diabetes, anterior STEMI.

  An ACEI such as enalapril, ramipril or lisinopril or if not tolerated due to ACEI related cough, an ARB such as valsartan, candesartan or losartan is recommended. ACEI and ARB act in preventing cardiac remodeling especially with LVEF <40%.
- **Mineralocorticoid receptor antagonist (MRA)** – spironolactone is given as add on therapy to ACEI or ARB if LVEF < 40%. Eplerenone can be given if troublesome antiandrogenic effects occur with spironolactone.

LV function should be measured in all patients with STEMI with a 2D echocardiogram. In post AMI patients with LVEF < 40% treatment with ACEI or ARB, MRA, specific BB and ivabradine reduce mortality. Amiodarone is useful to treat atrial fibrillation and ventricular tachycardia.

A PPI such as pantoprazole 40 mg nocte is recommended long term along with DAPT to prevent peptic ulcer. Ezetimibe may be added to a statin to achieve lipid goals. Medications to be given at discharge to all STEMI patients in the absence of contraindications are listed in Table 5.

Calcium channel blockers, nitrates, frusemide, vitamin E, nicorandil, and fish oil have no proven survival benefit in STEMI patients but may be used for specific indications. Non-steroidal anti-inflammatory drugs (NSAID) are harmful in AMI patients and should not be prescribed for analgesia. Coronary artery bypass graft surgery (CABG) should be considered for patients with a patent IRA but with unsuitable anatomy for PCI. P2Y12 inhibitor needs to be stopped 3-7 days prior to CABG.

D. Risk factors and life style modification

The major cardiovascular risk factors need identifying and correction. ACS Sri Lanka audit project showed a high prevalence of risk factors in AMI patients in SL with diabetes in 28%, hypertension in 45%, and current smoking in 35%. Goals of therapy include

- Diabetes – Goal of treatment is HBa1C <7.0
- Hypertension – Goal of treatment is BP < 130/ 80
- Hyperlipidemia – Goal of treatment is LDL < 70 mg/dl
- Smoking cessation advice needs to be given to all smokers.
- Obesity, diet and sedentary lifestyle need addressing.
- Enrolment in a cardiac rehabilitation program with dietary and lifestyle advice, exercise prescribing and monitoring recovery and resumption of activities of daily living.

E. Management of complications

Management of complications of AMI are not discussed in detail here. Complications such as cardiogenic shock, acute pulmonary edema and arrhythmias need intensive care management. Mechanical complications such as ventricular septal rupture or papillary muscle rupture need identification and early corrective surgery.

F. Quality indicators and clinical audit in STEMI

A gap between optimal guideline-based treatment and actual care of STEMI patients could exist in clinical practice. In order to reduce this gap, validated quality indicators need to be measured to improve STEMI care and patient survival [1, 2,10]. Suggested performance measures to be recorded for each STEMI patient and clinically audited by all physicians managing STEMI patients in SL are given in Table 6.

Table 5. Medications at discharge for STEMI patients

Low dose aspirin 75-100 mg
P2Y12 inhibitor such as clopidogre 175 mg or ticagrelor 90 mg twice daily
High intensity statin such as atorvastatin 40-80 mg
BB-carvedilol, metoprolol, bisoprolol, nebivolol, dose titrated
ACEI or ARB [not both together] dose titrated
MRA when LVEF <40% spironolactone or eplerenone dose titrated
PPI such as pantoprazole 40 mg

BB – Beta blocker, ACEI – Angiotensin converting enzyme inhibitor, ARB – Angiotensin receptor blocker, MRA – Mineralocorticoid receptor antagonist, LVEF – Left ventricular ejection fraction, PPI – Proton pump inhibitor

Table 6. Performance and quality measures in STEMI care

Timely diagnosis and reperfusion therapy	
FMC to ECG and diagnosis time <10 min	Yes/ No
ECG diagnosis to fibrinolysis time < 10 min	
Door to needle time for fibrinolysis < 30 min	
Door in door out time for PPCI transfer < 30 min	
FMC to device time when transferred for PPCI < 120 min	
FMC to device time when admitted directly to PCI enabled hospital < 90 min	
Immediate treatment in the absence of contraindications	
ECG monitoring with standby defibrillator	Yes/ No
Aspirin loading dose	
Clopidogrel loading dose	
Enoxaparin loading dose for fibrinolytic therapy	
Enoxaparin maintenance following fibrinolytic therapy	
High intensity statin	
Discharge medications in the absence of contraindications	
Low dose aspirin	Yes/ No
Clopidogrel	
High intensity statin	
BB	
ACEI or ARB	
MRA use in LVEF<40%	
PPI	
Investigations and risk factor management	
Cardiac troponin assay	Yes/ No
Pre discharge cardiology referral following fibrinolysis	
Pre discharge 2D echocardiogram	
HBA1c target achieved	
Blood pressure target achieved	
LDL cholesterol target achieved	
Body mass index documentation	
Smoking cessation advice given to smokers	
Referral to a cardiologist for all STEMI	
Enrolment in a cardiac rehabilitation program	

FMC – First medical contact, ECG – Electrocardiogram, PPCI – Primary percutaneous coronary intervention, BB – Beta blocker, ACEI – Angiotensin converting enzyme inhibitor, ARB – Angiotensin receptor blocker, MRA – Mineralocorticoid receptor antagonist, LVEF – Left ventricular ejection fraction, PPI – Proton pump inhibitor

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Neuropathic pain: current definition and review of drug treatment

Summary

Neuropathic pain is relatively common and often poorly treated.

Management options include tricyclic antidepressants or serotonin and noradrenaline reuptake inhibitors in the first instance, followed by pregabalin or gabapentin.

Tramadol or topical lidocaine (lignocaine) could be considered as second line. Stronger opioids have been relegated to third line.

It is important to remember that opioids and gabapentinoids have abuse potential.

Fibromyalgia and chronic low back pain without radiculopathy do not meet the current criteria for the definition of neuropathic pain.

Keywords: anticonvulsants, antidepressants, cannabinoids, neuropathic pain, opioids

*(Aust Prescr 2018; **41**: 60-3)*

Introduction

Neuropathic pain is associated with impaired quality of life, and is often poorly managed. Around 7-8% of adults have pain with neuropathic characteristics. A quarter of people with diabetes and 35% of people with HIV have neuropathic pain.[1]

The management of neuropathic pain can be challenging and, as with all pain, should be approached with a biopsychosocial framework. There are several options for drug treatment as part of an overall approach to improve patients' quality of life and function.[2]

International guidelines have clarified the definition of neuropathic pain and updated their recommendations for drug treatment based on evidence from a systematic review and meta-analysis.[3,4] Being aware of these changes is important in the clinical assessment and treatment.

A new definition for neuropathic pain

Neuropathic pain is now defined by the International Association for the Study of Pain (IASP) as 'pain caused by a lesion or disease of the somatosensory nervous system'.[3] This replaces the older definition of 'pain initiated or caused by a primary lesion, dysfunction or transitory perturbation of the peripheral or central nervous system'. The definition was reviewed and updated because the term dysfunction in the old definition was thought to be over-inclusive and did not reflect the pathophysiology. Additionally, neuropathic pain is not one disease entity but a number of diseases or lesions with a cluster of symptoms and signs, where understanding of pathophysiology is evolving.[5]

Proponents of the change believe it has greater scientific rigour. It removes confusion around pain arising as a result of disease within the nervous system but outside the somatosensory system, for example pain from muscle spasticity. It now excludes syndromes where pathophysiology is unclear, such as fibromyalgia or complex regional pain syndrome, which is controversial and has been perceived by some to be overly restrictive.[6]

Primary disease management

The primary disease management of neuropathic pain needs to consider the individual as a whole. For instance, in patients with diabetic neuropathy, erratic glycaemic control worsens symptoms and improving glycaemic control may reduce progression of neuropathy. However, there is increased mortality with intensive insulin regimens in patients with established diabetic neuropathy compared to patients without neuropathy.[7] HIV associated neuropathy presents an even more complex picture – starting antiretrovirals may initially improve symptoms although nerve damage may progress. Some antiretrovirals can cause neuropathy, and neurotoxicity may be a feature of concomitant medicines such as isoniazid for tuberculosis.[8,9]

Drugs for neuropathic pain

The IASP's Neuropathic Pain Special Interest Group (NeuPSIG) has recently undertaken a systematic review of medicines for neuropathic pain (Table).[4] Fibromyalgia, atypical facial pain, complex regional pain syndrome and chronic low back pain without radiculopathy were not included in the review as they do not meet the current criteria for the definition of neuropathic pain.

The review included tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors (SNRIs), antiepileptic drugs, opioids, topical lidocaine (lignocaine), capsaicin high-concentration patches and oromucosal cannabinoids. A number of overarching themes were identified:

Table **Drug treatment for neuropathic pain – updated recommendations from the International Association for the Study of Pain**

Recommendation	Drugs
First-line	SNRI - duloxetine, venlafaxine
	Tricyclic antidepressants
	Gabapentin, pregabalin
Second-line	Capsaicin 8% patches
	Lidocaine (lignocaine) patches
	Tramadol
Third-line	Strong opioids

SNRI serotonin noradrenaline reuptake inhibitors
Adapted from reference 4.

- most studies were conducted in diabetic neuropathy or postherpetic neuralgia
- publication bias accounted for approximately 10% of the treatment effect
- placebo effect was large
- drug effects were modest[4]
- data did not identify that one particular drug or drug class was superior in any particular neuropathic pain syndrome
- the majority of studies were for 12 weeks or less
- data were limited to non-cancer pain in adults.

Antidepressants

Tricyclic antidepressants and SNRIs were effective in reducing pain. Amitriptyline was the most studied tricyclic antidepressant (daily doses 25-150 mg) and did not show a dose-response effect. Seven of nine studies with duloxetine 20-120 mg were positive, while two of four studies identified efficacy with venlafaxine 150-225 mg daily. The negative venlafaxine studies were at lower doses.

Antiepileptics

Most trials with pregabalin (18/25) showed improvement in neuropathic pain, and the effect was greater with larger doses. Pregabalin in HIV neuropathy was no better than placebo. However, the placebo was very effective. Gabapentin was also found to be effective, although no dose response was identified. The number needed to harm was 13.9 for pregabalin and 25.6 for gabapentin. Other antiepileptic drugs had minimal evidence of efficacy, and topiramate, carbamazepine and oxcarbazepine had a poor safety profile.

Tramadol, tapentadol and opioids

Tramadol consistently showed efficacy, while tapentadol had very limited supporting data. With morphine or oxycodone, 10 of 13 trials showed benefit, with no benefit in increasing the dose beyond 180 mg daily oral morphine equivalents.

Topical treatments

There were some limited data suggesting the efficacy of lidocaine (lignocaine) 5% patches, with good safety and tolerability. Although registered, this product is not available on the Pharmaceutical Benefits Scheme (PBS) 10 so may be prohibitively expensive for patients.

For postherpetic neuralgia and HIV neuropathy, a high-concentration (8%) capsaicin patch demonstrated efficacy over a low-dose (0.04%) patch. Unfortunately the high-dose patch is not available in Australia.

Oromucosal cannabinoids

The meta-analysis identified mostly negative data for a fixed-dose combination of cannabidiol and 9-tetrahydrocannabinol (nabiximols) in reducing pain in multiple sclerosis.[4] A statement by the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists on medicinal cannabis identifies no role for the use of cannabinoids in neuropathic pain, but notes pain and spasticity related to multiple sclerosis may be an exception.[11]

Trigeminal neuralgia

Trigeminal neuralgia is the only condition in which a specific drug class has shown superior efficacy.

Carbamazepine and oxcarbazepine are first line for pharmacological pain management.[12]

It is currently recommended that Asian people of non-Japanese origin are tested for the HLA-B*1502 allele as this confers an increased risk of cutaneous drug reactions with carbamazepine.[13]

Interventional modalities

Local nerve blocks, spinal or epidural medicines, and neuro-ablative, neuromodulatory and neurosurgical procedures are also used for neuropathic pain.[14]

Updated recommendations for treatment

As a result of the meta-analysis, NeuPSIG has updated its recommendations for the treatment of non-cancer associated neuropathic pain in adults. With the exception of trigeminal neuralgia, there were no data identifying that any particular drug was superior to another in any particular disease state.[4]

The guidelines recommend tricyclic antidepressants, gabapentin or pregabalin, and the SNRIs venlafaxine or duloxetine as first line.[4]

Second-line treatments include tramadol. Topical lidocaine (lignocaine) or high-concentration capsaicin may be considered for neuropathic pain when there is a presumed local generator.[4]

The consensus is that opioids can no longer be recommended as first-line treatment, and there is general agreement that they should only be considered as third line, with appropriate monitoring for safety and efficacy.[4] It is increasingly recognised that the harms of opioids, in particular addiction, cannot be adequately identified in short-term studies. Also, these short-term studies could not identify if any benefit persists or is lost as tolerance develops.

A pragmatic approach to drug therapy

Choose a tricyclic antidepressant or SNRI with consideration of the patient's comorbidities, potential drug interactions and adverse effects, and consider pregabalin or gabapentin next before tramadol. There is a paucity of guidance on duration of treatment. Again, a pragmatic approach may be to try a therapy for 12 weeks as this is the maximum duration of most of the trials. Monitor for efficacy (using multidimensional tools for pain intensity, quality of life and patient function) and safety, and stop if the treatment is not working.

The PBS listing for pregabalin in neuropathic pain is that 'the condition must be refractory to treatment with other drugs'. Cost of treatment is significant. In 2016-17, more than 3.5 million PBS scripts for pregabalin were issued at a cost of over $190 million.[15] Gabapentinoids have neurocognitive adverse effects, can cause weight gain and are associated with an increased risk of falls. They are anxiolytic, and there is emerging evidence of significant pregabalin abuse.[16]

Any consideration of psychotropic drugs including gabapentinoids or opioids (tramadol or stronger opioids) should involve:

- assessing the risk of abuse, including history of psychiatric, personality or substance use disorder
- ongoing monitoring for development of abuse
- multidimensional assessment of efficacy.

A plan to stop therapy should be discussed with the patient before treatment starts, and daily opioid doses should not exceed 60 mg oral morphine equivalents without specialist review.[17]

Conclusion

A well-conducted meta-analysis reviewing drug treatment of neuropathic pain provides clear recommendations. Tricyclic antidepressants and SNRIs should be trialled first. If they are ineffective, consider a trial of a gabapentinoid then tramadol. This should be accompanied by multi-dimensional assessment of efficacy, review for harms associated with treatment and a plan for stopping treatment if there is no benefit.

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