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HEART & STROKE FOUNDATION
Canadian Partnership
for Stroke Recovery

Chapter 17: Medical Complications Post Stroke

Abstract

Medical complications post stroke are defined as medical or neurological problems that necessitate a physician's order and require monitoring by medical staff (Chen et al., 2014; Dromerick & Reding, 1994). These complications are separate from issues related to secondary stroke prevention, occur relatively frequently, and contribute to poor health outcomes (Doshi et al., 2003). Although the number of potential medical complications can be extensive for a given patient, this review focuses on the most common and clinically relevant medical complications in the short- and long-term: bladder and bowel dysfunction, venous thromboembolism, seizures, osteoporosis, central pain states, fatigue, and insomnia. Therefore, an understanding of these disorders is critically important to stroke care and management.

Norine Foley, MSc
Joshua Wiener, PhD Candidate
Andreea Cotoi, MSc
Jerome Iruthayarajah, MSc
Norhayati Hussein, MBBS
Emma A. Bateman, MD
Robert Teasell, MD

Key Points

Medical Complications

- Medical complications are common post stroke, occurring in 44-96% of patients.

- Post-stroke complications include cardiovascular complications (e.g. myocardial infarction, venous thromboembolism), pulmonary complications (e.g. pneumonia), urinary/bowel complications (e.g. incontinence, constipation, urinary tract infections), complex pain (e.g. hyperalgesia), and mood disorders (e.g. depression).

Bladder and Bowel Dysfunction

- Urinary incontinence is a common complication post stroke, especially during acute care.

- Poor functional independence post stroke is a risk factor for urinary incontinence.

- Urinary incontinence post stroke is associated with poor outcomes including slower recovery, prolonged hospitalization, and low health-related quality of life.

- Urinary incontinence post stroke can be related to a variety of direct (i.e. damaged neuromicturition pathways) and indirect (i.e. motor, cognitive, and language deficits) factors.

- Diagnosis of urinary incontinence post stroke should be made based on clinical history and physical examination. Additional investigations such urodynamic studies can be pursued to guide diagnosis when needed.

- Pelvic floor training may be an effective intervention for urinary incontinence post stroke.

- Despite several pharmacological interventions for urinary incontinence, namely anticholinergic medications, there is no evidence of their effectiveness in a stroke-specific population.

- Further research is required for the effectiveness of complementary/alternative therapies as well as electromechanical devices in treating urinary incontinence post stroke.

- Catheterization is an effective intervention for urinary incontinence post stroke, but chronic catheter use is associated with adverse events and poor outcomes.

- Further research is required to examine processes to optimize catheter removal, such as bladder reconditioning.

- Bowel dysfunction is a common complication post stroke, although it may be more directly related to non-stroke factors.

- There is limited research regarding treatments for constipation and fecal incontinence post stroke.

Venous Thromboembolism

- Deep vein thrombosis is diagnosed using venous Doppler ultrasound, D-dimer assay, and/or venography.

- Pulmonary embolism is diagnosed using ventilation-perfusion scanning, CT pulmonary angiography, and/or traditional pulmonary angiography.

- Deep vein thrombosis and pulmonary embolism are common and serious post-stroke complications.

- It is unclear whether low molecular weight heparin and unfractionated heparin are effective in preventing venous thromboembolism post stroke, without an increased risk of bleeding complications. However, the efficacy of these medications has been demonstrated in non-stroke populations.

- Intermittent pneumatic compression may prevent the development of deep vein thrombosis post stroke, while graded compression stockings may not be an effective prophylactic intervention.

- Venous thromboembolism may be treated with heparinoids or novel oral anticoagulants (e.g. dabigatran, rivaroxaban), although the research evidence is not specific to stroke.

Seizures

- Post-stroke seizures occur is a less common complication post stroke, although the rates vary widely across studies and stroke onset.

- Common risk factors for post-stoke seizures include cortical strokes, severe strokes, greater disability, and younger age.

- The majority of seizures post stroke are simple partial seizures.

- Post-stroke seizures appear to be more common in hemorrhagic and cortical strokes, although this may be more directly related to stroke severity rather than etiology or location.

- Insufficient evidence exists to guide selection of monotherapy for antiepileptic medications in patients with post-stroke seizures. Treating all stroke patients with anticonvulsants as primary seizure prophylaxis is not recommended. Decisions to initiate antiepileptic therapy should be tailored to patients' individual needs.

Osteoporosis

- Osteoporosis is a common complication post stroke, particularly in the hemiparetic limbs.

- Compared to osteoporosis in the general population, post-stroke osteoporosis is associated with a considerably greater loss of bone mineral density.

- Risk factors for post-stroke osteoporosis include severity of hemiplegia, duration of immobility, and vitamin D deficiency.

- Hip fractures are a common occurrence post stroke and associated with greater risk of morbidity/mortality. They are related to high rates of osteoporosis, increased risk of falls, and poorer mobility post stroke.

- Treatment with bisphosphonates or vitamin D derivatives may help to preserve bone density post stroke, although their impact on associated fractures is unclear.

- Further research is required to determine the effect of treatment with vitamin B, vitamin K, and calcitonin on post-stroke osteoporosis and associated fractures.

Central Pain States

- Central post-stroke pain is a less common complication post stroke, although prioritization of other conditions may lead to its underdiagnosis.

- The precise pathophysiology of central post-stroke pain is unknown, but it appears to be associated with a lesion involving the spino-thalamo-cortical pathway.

- Central-post stroke pain generally involves some form of spontaneous and evoked sensory abnormality on the affected side including dysesthesia, allodynia, and hyperalgesia.

- Development of central post-stroke pain is most often within the first month of stroke onset.

- A wide range of pharmacological interventions are available for the treatment of central pain post stroke, including anticonvulsants, antidepressants, anesthetics, and narcotics. However, the majority of these require further research to determine their effectiveness in pain reduction.

- Repetitive transcranial magnetic stimulation may be effective in reducing central pain post stroke when delivered at higher frequencies, although further research is required.

Fatigue

- Fatigue is a common condition post stroke, although there is variation in reported rates.

- Risk factors for post-stroke fatigue include depression, chronic pain, and sleep disorders; it may be associated with poor recovery.

- Modafinil and OSU-6162 may be effective treatments for post-stroke fatigue, while antidepressants have not demonstrated efficacy.

- Cognitive therapy, graded activity training, and mindfulness-based stress reduction may be effective treatments for post-stroke fatigue, while fatigue management programs have not demonstrated efficacy.

Insomnia

- Acupuncture may be an effective treatment for insomnia post stroke, although further research is required.

Dr. Robert Teasell
Parkwood Institute, 550 Wellington Road, London, Ontario, Canada, N6C 0A7
Phone: 519.685.4000 ● Web: www.ebrsr.com ● Email: Robert.Teasell@sjhc.london.on.ca

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17.1 Frequency of Medical Complications Post Stroke

Medical complications are common after acute stroke and contribute to adverse patient outcomes, delayed functional recovery, as well as increased morbidity and mortality. Complications post stroke are defined as medical or neurological problems that necessitate a physician's order and require monitoring by medical staff (Chen et al., 2014; Dromerick & Reding, 1994). Reports of the percentage of patients experiencing one or more medical complications after acute stroke vary widely, from 44 to 95% (McLean, 2004). Complications tend to occur more frequently in older patients and patients with more severe strokes (Davenport et al., 1996).

These complications are separate from issues related to secondary stroke prevention, occur relatively frequently, and contribute to poor health outcomes, despite being potentially treatable (Doshi et al., 2003). For instance, the development of medical complications in acute care may result in delayed transfer to inpatient stroke rehabilitation. In a cohort of 2,457 consecutively admitted patients with acute stroke, Roth et al. (2007) reported that post-stroke medical complications were the single greatest factor in a model for determining the number of days between stroke onset and admission to rehabilitation, accounting for 17.3% of the variance. In this study, the most common complications contributing to the delay were pneumonia and urinary tract infections (UTI) (Roth et al., 2007).

Medical complications can affect one or many body systems, including but not limited to depression, delirium, falls, fractures, constipation, gastrointestinal bleeding, congestive heart failure, myocardial ischemia, urinary incontinence, and pneumonia. While the number of potential medical complications can be extensive for an individual patient, this review focuses on the most common and clinically significant medical complications in the short- and long-term: urinary and fecal incontinence, venous thromboembolism, seizures, osteoporosis, central pain states, fatigue, and insomnia. Understanding the complications after acute stroke is crucial to preventing, identifying, and treating them in order to reduce adverse patient outcomes.

Table 17.1.1 Incidence of Common Medical Complications

Author, Year Sample Size	Complication (%)
Dromerick & Reding (1994) N=100	Inpatient stroke rehabilitation: • Urinary tract infection (44%) • Urinary retention (25%) • Pneumonia (7%) • Pulmonary embolus (0%) • Deep vein thrombosis (4%) • Musculoskeletal pain (31%) • Fall (25%) Average number of medical complications per patient: 3.6 • At least one medical complication occurred in 96% of patients • 13% of patients required transfer to acute care due to medical complications • 1% of patients died
Kalra et al. (1995) N=245	Stroke unit vs General medical ward: • Urinary tract infection (17% vs 33%, p<0.01) • Urinary catheterization (7% vs 18%, p<0.01) • Aspiration (33% vs 20%, p<0.01) • Chest infection (8% vs 16%, p<0.05) • Deep vein thrombosis (3% vs 7%, NS) • Musculoskeletal pain (38% vs 23%, p<0.05) At least one medical complication occurred in 60% of patients • 7.8% of patients died
Davenport et al. (1996)	Acute care hospital:

N=613	• Urinary tract infection (16%) • Chest infection (12%) • Deep vein thrombosis (3%) • Fall (22%) • Fracture (3%) • Epileptic seizure (4%) At least one medical complication occurred in 59% of patients • 22.1% of patients died in hospital
Johnston et al. (1998) N=279	Acute care hospital: • Urinary tract infection (11%) • Pneumonia (all types) (10%) • Aspiration pneumonia (6%) • Deep vein thrombosis (2%) • Congestive heart failure (11%) • Angina/myocardial infarct/cardiac ischemia (6%) • Gastrointestinal bleed (5%) • Seizure (3%) At least one medical complication occurred in 95% of patients • 14% of patients died within 3 months of stroke onset
Langhorne et al. (2000) N=311	Acute care hospital: • Urinary tract infection (23%) • Chest infection (22%) • Pulmonary embolism (1%) • Deep vein thrombosis (2%) • Pain, shoulder (9%) • Pain, non-shoulder (34%) • Pressure sore (21%) • Fall (25%) At least one medical complication occurred in 85% of patients • 19% of patients died in hospital
Roth et al. (2001) N=1029	Inpatient stroke rehabilitation, Proportion transferred to acute care: • Urinary tract infection (30.5%, 3.2%) • Pneumonia (4.0%, 47.6%) • Deep vein thrombosis (4.1%, 83.3%) • Pulmonary embolism (1.1%. 60%) • Peptic ulcer disease and gastrointestinal bleed (3.1%, 48.4%) • Seizure (1.5%, 80%) At least one medical complication occurred in 75% of patients • 19% of patients required transfer to acute care due to medical complications • 0.3% of patients died
Doshi et al. (2003) N=140	Inpatient stroke rehabilitation: • Urinary tract infection (14.3%) • Urinary retention (20.9%) • Deep vein thrombosis (0.7%) • Pulmonary embolism (0%) • Constipation (22.9%) • Seizure (0.7%) At least one medical complication occurred in 54.3% of patients • There were no reported deaths
McLean (2004) N=133	Inpatient stroke rehabilitation: • Urinary tract infection (15%) • Pneumonia (2%) • Depression (26%) • Fall (20%) • Shoulder pain (24%) • Shoulder-hand syndrome (1.5%)

	• Seizure (1.5%) At least one medical complication occurred in 67% of patients • 2.3% of patients died
Hung et al. (2005) N=346	Inpatient stroke rehabilitation: • Urinary tract infection (13.6%) • Pneumonia (4.9%) • Depression (9.3%) • Pressure sore (1.5%) • Seizure (1.2%) At least one medical complication occurred in 44% of patients • 2.9% of patients required transfer to acute care due to medical complications • 0.3% of patients died
Kitisomprayoonkul et al. (2010) N=118	Inpatient stroke rehabilitation: • Urinary tract infection (17.8%) • Pneumonia (4.2%) • Depression (56.6%) • Musculoskeletal pain (28%) • Complex Regional Pain Syndrome-1 (15.3%) At least one medical complication occurred in 70.3% of patients • 11.8% of patients required transfer to acute care due to medical complications
Rohweder et al. (2015) N=244	Acute care hospital: • Urinary tract infection (28%) • Myocardial infarction (7%) • Pulmonary embolism (1.2%) • Chest infection (17%) • Other infection (13%) • Fall (29%) • Pain (57%) The frequency of death was not reported

Discussion

Numerous studies have investigated the incidence of medical complications after stroke of multiple etiologies in a variety of settings, including acute care, inpatient rehabilitation, and after discharge. As summarized in Table 17.1.1, these studies report varying rates of medical complications. The discrepancies in medical complication rates is likely multifactorial, including different study designs, varying diagnostic criteria for medical complications, pre-selection of complications to be studied, different patient selection methods, differences between the acute care and inpatient rehabilitation setting, and inherent differences in the populations studied, such as country of origin. Moreover, potential sources of bias can confound the accurate reporting of complications. Retrospective identification of complications, case note retrieval bias (i.e. obtaining information about patients who may have deceased earlier), and inter-observer bias (i.e. the ability of one or more observers to accurately retrieve medical information from patient records) may be factors contributing to the variability of complication reporting (Davenport et al., 1996).

In a large, prospective, multicentre cohort study in Scotland, UK, Langhorne et al. (2000) reported that that the majority of complications experienced during acute care hospital stay included pressure sores, pain, and infections. In this study, approximately 85% of patients experienced at least one pre-specified complication during their time in hospital after acute stroke (Langhorne et al., 2000). In a randomized, retrospective study comparing complication rates between a general medicine ward and specialized stroke unit in patients two weeks post stroke, Kalra et al. (1995) reported that patients admitted to a specialized stroke unit within acute care had fewer UTIs, chest infections, episodes of aspiration, and musculoskeletal pain compared with patients admitted to general wards.

In a single-centre prospective cohort study of 1029 patients in inpatient stroke rehabilitation in Chicago, USA, Roth et al. (2001) reported that 75% of patients experienced at least one medical complication during their inpatient rehabilitation stay. UTIs, depression, falls, soft tissue pain, and elevated blood pressure were the most common complications; 19% of patients required transfer back to acute care for the management of medical complications. In this study, patients most likely to experience a complication post stroke were those with greater severity of stroke and a history of hypertension. Both McLean (2004) and Kitisomprayoonkul et al. (2010) found UTIs, depression, and musculoskeletal pain to be common, but they reported much lower frequency of certain medical events than in other studies, specifically pneumonia, seizures, gastrointestinal disturbances, and pressure ulcers.

In a prospective study of 133 patients admitted to an inpatient stroke rehabilitation centre in Nova Scotia, Canada, McLean (2004) reported that 67% of patients experienced at least one complication post stroke, and 25% experienced two or more complications. The most frequently reported complications in their study were depression (26%), shoulder pain (24%), falls (20%), and UTIs (15%). The author also suggested that certain patient characteristics such as age, disability before stroke onset, and stroke severity may predict the likelihood of complications post stroke. In a prospective study of 118 patients admitted to inpatient rehabilitation in Bangkok, Thailand, Kitisomprayoonkul et al. (2010) found that 70.3% of patients experienced at least one medical complication. Depression was the most commonly reported complication, occurring in 56.6% of patients. The only consistent predictive factor for complications post stroke between these studies was initial severity of stroke (Kitisomprayoonkul et al., 2010; McLean, 2004; Roth et al., 2001).

Within acute care, medical complications were frequent in patients post stroke, ranging from 59% to 95% (Davenport et al., 1996; Johnston et al., 1998). For patients admitted for inpatient stroke rehabilitation in tertiary rehabilitation centres, the rates of medical complications post stroke were also high, ranging from 44% to 96% (Dromerick & Reding, 1994; Hung et al., 2005). Of these patients, 2.9-19% required transfer to an acute care hospital for diagnosis, treatment, or management (Hung et al., 2005; Roth et al., 2001). Although the relative frequency of each complication differs between these two settings, the high incidence of medical complications post stroke clearly has implications for rehabilitation.

Conclusions Regarding the Frequency of Medical Complications Post Stroke

- Medical complications are common post stroke, occurring in 44-96% of patients.

- Post-stroke complications include cardiovascular complications (e.g. myocardial infarction, venous thromboembolism), pulmonary complications (e.g. pneumonia), urinary/bowel complications (e.g. incontinence, constipation, urinary tract infections), complex pain (e.g. hyperalgesia), and mood disorders (e.g. depression).

17.2 Bladder Dysfunction Post Stroke

17.2.1 Prevalence, Predictors, and Consequences of Urinary Incontinence Post Stroke

Urinary incontinence (UI) is a common problem following stroke: its incidence ranges from 21% to 79% (Brittain et al., 1999; Doshi et al., 2003; Sreeraj et al., 2012; van Kuijk et al., 2001).

However, UI post stroke usually resolves spontaneously (without intervention or treatment) within 8 weeks of stroke onset (Borrie et al. 1986; Brocklehurst et al. 1985). Of all patients experiencing UI post stroke, 14-19% may develop UI that persists at 6 months post stroke (Barer, 1989; Nakayama et al., 1997). UI tends to be most frequent in patients with more severe strokes and in patients with pre-morbid incontinence (Brittain et al., 1999; Nazarko, 2003). Normal age-related changes in bladder function may also independently affect recovery (Marinkovic & Badlani, 2001).

In patients with previously normal bladder function, other risk factors for developing UI post stroke vary by study. Brittain et al. (1999) implicated persistent stroke-related motor weakness, sensory abnormalities, altered level of consciousness, and cognitive impairment as risk factors for incontinence, whereas Jorgensen et al. (2005) identified depression, lower extremity motor weakness, and cognitive impairment. Gariballa (2003) found that patients with UI at admission tended to be older, more undernourished/dehydrated, more impaired, and at greater risk for infective complications than patients without UI. As well, Williams et al. (2012) reported that older age, female sex, pre-stroke UI, and severe stroke were independent predictors of UI at 12 months.

Discrepancies in the reported rates and contributing factors likely arise from differing definitions of incontinence, timing of assessment, survey methods, and populations under study. Furthermore, variable reporting may reflect the fact that UI is common even amongst healthy elderly persons, particularly women (Brooks, 2004). The prevalence of UI in women is estimated at 1.3 to 4.5 times greater than in men (Jorgensen et al., 2005). In general, UI is divided into three types: urge urinary incontinence (UUI), stress urinary incontinence (SUI), and mixed urged and stress urinary incontinence. Estimates of the incidence of all types of pre-stroke UI range from 17-22% (Benbow et al., 1991; Borrie et al., 1986). UUI, often a manifestation of abnormal volitional control of bladder function, is the most common type post stroke (Brittain et al., 1999; Brooks, 2004), although a stroke can exacerbate pre-existing SUI (Brooks, 2004).

A study of patients with acute stroke demonstrated that significant risk factors for post-stroke UI included age, stroke severity, diabetes, and comorbidity associated with other pre-existing disabling diseases (Nakayama et al., 1997). Recovery from post-stroke UI is associated with less disability and lower rates of institutionalization than persistent incontinence (Patel et al., 2001a). In fact, Bean et al. (2003) noted an almost two-fold difference in level of disability post stroke among those who were incontinent compared to those were continent (p<0.001). Another study found that patients suffering from UI on admission had greater morbidity and mortality throughout their hospital stay and at 3 months post stroke (Gariballa, 2003). As noted by several investigators (Jawad et al., 1999; Jongbloed, 1986; Reding et al., 1987), recurring incontinence denotes a poor long-term prognosis for functional recovery.

In another study regarding the impact of UI post stroke, Kolominsky-Rabas et al. (2003) examined the occurrence of UI and the long-term effect it had on institutional status within a community-based population. Throughout the acute phase 41% of patients had full UI, 12% had partial UI, and 47% had no UI (16%, 16%, and 68% respectively at 12-months follow-up). In total, patients institutionalized at 12-months follow-up included 45% of patients with UI compared to only 5% of patients without UI. The authors concluded that the risk of institutionalization 1-year post stroke is a "fourfold higher" for stroke patients with UI in the acute phase of rehabilitation.

Few investigators have examined the prevalence of UI past the acute and subacute stage of stroke. Brittain et al. (2000) reported that a significantly higher proportion of community-dwelling individuals who experienced a stroke had more urinary symptoms compared to those that had never had a stroke (64% vs. 32%); the difference was statistically significant even after adjusting for differences in age and sex between groups. Those who experienced stroke were 1.77 times more likely to experience urinary symptoms than those who did not, and twice as many individuals

post stroke reported that their urinary symptoms were moderate to severe. As well, more individuals who experienced stroke reported a significant impact of urinary symptoms on lifestyle.

Among another sample of community-dwelling individuals post stroke, Jorgensen et al. (2005) reported that 17% were incontinent compared with a non-stroke control group, with whom the prevalence was 7%. The study tracked subjects an average of nine years post stroke and found that UI was associated with depression, poor leg motor function, and impaired cognition. Ersoz et al. (2013) found a statistically significant difference with respect to age and marital status regarding the frequency of regaining spontaneous voiding (SV) in chronic stroke patients. Geriatric patients ($\geq$ 65 years old) were less likely to experience SV compared to their younger stroke patient counterparts (50% vs. 75.5%). In addition, once discharged home, married stroke patients were found to have a statistically significant higher SV frequency compared to single/divorced patients (79% vs. 47%).

Table 17.2.1.1 Prevalence of Urinary Incontinence Post Stroke

Author, Year Sample Size	Prevalence (%)
Brocklehurst et al. (1985) N=135	• 39% at admission to acute care • 25% at 6 months post stroke • 15% at 1 year post stroke • 23% at 2 years post stroke
Wade et al. (1985) N=532	• 44% at admission to acute care
Borrie et al. (1986) N=151	• 60% at admission to acute care • 29% at 3 months post stroke
Fullerton et al. (1988) N=205	• 64% at admission to acute care
Ween et al. (1996) N=432	• 41% at admission to inpatient rehabilitation (mean 16 days)
Kalra et al. (1993) N=96	• 79% at admission to acute care
Nakayama et al. (1997) N=935	• 47% at admission to acute care • 28% at discharge from acute care • 19% at 6 months post stroke
Brittain et al. (2000) N_{Total}=10226 N_{Stroke}=423	• 64% in community-dwelling persons post stroke
Patel et al. (2001b) N=235	• 40% at 10 days post stroke • 19% at 3 months post stroke • 15% at 1 year post stroke • 10% at 2 years post stroke
Kolominsky-Rabas et al. (2003) N=752	• 41% at admission to acute care
Jorgensen et al. (2005) N_{Stroke}=213 NH_{ealthy}=242	• 17% in community-dwelling persons post stroke (mean 9 years)
Ersoz et al. (2007) N=110	• 27% in inpatient rehabilitation (mean 6 months)
Wilson et al. (2008) N=~22000	• 39-44% at 1 week post stroke • 15-20% at discharge
Kovindha et al. (2009) N=185	• 12.4% at admission to inpatient rehabilitation (mean 2 weeks) • 8.1% at discharge (mean 6 weeks)

Williams et al. (2012) N=340	• 43.5% at 3 months post stroke • 37.7% at 12 months post stroke
Sreeraj et al. (2012) N=486	• 29.4% at admission to acute care
Kuptniratsaikul et al. (2013) N=214	• 14.4% at admission to inpatient rehabilitation (mean 24 days) • 4% at 12 months post stroke
Cai et al. (2015) N=711	• 44.3% during stay at neurological unit

Discussion

The risk factors for UI post stroke vary by study, which may reflect diverse patient populations, different evaluation time post stroke, and different definitions of UI. However, some common themes emerge with regards to stroke and personal factors that increase risk of UI post stroke. In a prospective cohort study, Pizzi et al. (2014) studied 106 patients admitted to a neurorehabilitation service after ischemic stroke. The authors found that UI developed in 79% of patients and that it was strongly associated with lower functional status or greater stroke area, as measured by the Functional Independence Measure (FIM). Similarly, Gelber et al. (1993) found that patients with UI had lower Barthel Index and Modified Barthel Index scores at admission and discharge, and were more likely to have aphasia. In a prospective study of 423 patients with ischemic or hemorrhagic stroke admitted to inpatient rehabilitation, Ween et al. (1996) found that UI was associated with lower FIM scores, poorer motor function, and the presence of dysphagia. The authors found that small vessel, also known as lacunar, strokes had the lowest rates of UI and that pre-existing comorbidities were not predictive of UI. As well, UI was strongly associated with slower and reduced extent of recovery post stroke compared to continent controls.

In a retrospective case control study, the Overactive Bladder Symptom Score (OABSS) was used to examine the prevalence and risk factors of post-stroke overactive bladder in 500 patients with chronic stroke (Itoh et al. 2013). Patients were stratified by the presence or absence of symptoms for overactive bladder (OAB), and independent risk factors for OAB were examined using logistic regression methods. Patients with symptoms of OAB had significantly lower health-related quality of life compared to patients who did not report any symptoms of OAB. This study found that 73% of patients with symptoms of OAB had never been treated for their symptoms, despite relatively high OABSS scores (mean 7.1), indicating significant burden of symptoms. Unlike previous studies, Itoh et al. (2013) did not find that motor deficits or sensory disturbances were predictive of UI.

Several of the studies reviewed above outlined negative patient consequences associated with UI and its sequelae: UTIs; higher risk of skin breakdown; higher risk of falls; poorer health-related quality of life; slower and reduced extent of recovery; likelier discharge to a long-term care facility; and prolonged hospitalization (Gelber et al., 1993; Ifejika-Jones et al., 2013; Mehdi et al., 2013; Pizzi et al., 2014; Ween et al., 1996). Despite the negative effects on patients and their caregivers, Itoh et al. (2013) found that many patients with significant symptoms had never been treated for their UI.

Conclusions Regarding Prevalence, Predictors, and Consequences of Urinary Incontinence Post Stroke

- Urinary incontinence is a common complication post stroke, especially during acute care.

- Poor functional independence post stroke is a risk factor for urinary incontinence.

- Urinary incontinence post stroke is associated with poor outcomes including slower recovery, prolonged hospitalization, and low health-related quality of life.

17.2.2 Pathophysiology of Urinary Incontinence Post Stroke

Normal Bladder Function
Normal bladder function requires a compliant bladder and competent urethral sphincters. The bladder is a predominantly muscular structure: the detrusor muscle relaxes to accommodate and store urine, and contracts to expel it via the urethra (Mehdi et al., 2013). The actions of the detrusor muscle must be coordinated with the urethral sphincter, two muscles that control the opening of the urethra, the outflow tract for urine (Borrie, 1998). This coordination and the normal control of voiding involve complex interplay of the brain, brainstem, spinal cord, and peripheral sympathetic, parasympathetic, motor, and sensory nerves.

The sympathetic nervous system relaxes the detrusor muscle to allow for bladder filling. During filling, the internal urethral sphincter is tonically active due to sympathetic innervation via alpha-receptors, closing the urethra to keep urine in the bladder. Normally, humans are unaware of bladder fullness until the bladder contains approximately 300 mL of urine. At this point, sensory afferent pelvic nerves relay the fullness sensation to the sacral spinal cord, where reflexes coordinate to strengthen the sympathetic input to the internal urethral sphincter and stimulate the contraction of the external urethral sphincter via the pudendal nerve. At the same time, these reflexes also inhibit parasympathetic activity, which is normally responsible for causing contraction of the detrusor muscle. Together, these actions mediate continence in the presence of a relatively full bladder.

Once that fullness reaches a critical level, the sensory afferent pelvic nerves intensify their signal to the spinal cord, which relays to the pontine micturition centre in the brainstem. The pontine micturition centre has the ability to inhibit the sympathetic nerves responsible for retaining urine while simultaneously activating the parasympathetic nerves responsible for contracting the detrusor muscle: the net effect is to stop bladder filling, relax the internal and external urethral sphincters to open the urethra to the flow of urine, and contract the bladder to actively expel urine. However, the pontine micturition centre is under higher levels of control, particularly via the pre-frontal cortex and other frontal lobe structures. When not socially acceptable or when not desired, the frontal lobe can prevent the pontine micturition centre from initiating urination. This higher-level control has its limits, however, and the pontine micturition centre or spinal cord reflexes will empty the bladder when the bladder reaches absolute maximum stretch as a protective mechanism against tissue damage, regardless of frontal lobe inputs.

Urinary Incontinence
A stroke can contribute to UI by altering a number of the structures involved in the complex control of urination, particularly the frontal lobe and pontine micturition centres, or the communication between these two structures: 1) UUI and bladder hyperreflexia (detrusor muscle overactivity) caused by disrupted neuromicturition pathways; 2) incontinence from stroke-related motor, cognitive, and language deficits despite normal bladder function; and 3) overflow incontinence and bladder hyporeflexia due to concurrent neuropathy or medications unrelated to the acute stroke.

In a systematic review of post-stroke UI literature, Mehdi et al. (2013) expanded the number of causes and types of UI post stroke to include six contributory mechanisms: 1) Direct damage to neuromicturition pathways due to the stroke lesion, particularly if it affects the frontal lobe, causes the detrusor muscle to contract without cortical inhibition, leading to UUI. These patients tend to present with urgency and involuntary leakage of urine. 2) Detrusor hyporeflexia, which may be due to initial loss of bladder tone, pre-existing neuropathy, or other non-stroke factors, leads to overflow incontinence. These patients present with dribbling or continuous leakage of urine in the setting of urinary retention or incomplete bladder emptying. 3) Reduced ability to identify bladder fullness, leakage, or both, leads to impaired awareness UI. These patients tend to have anterior circulation strokes with parietal or subcortical involvement, but without prominent frontal lobe involvement. 4) Consequences of stroke, such as communicative, cognitive, or motor abnormalities, indirectly cause incontinence despite intact bladder function by functionally limiting a patient's ability to perform tasks required to maintain continence, such as ambulating or asking for assistance. 5) Pre-existing stress incontinence, caused by weak pelvic floor muscles, is exacerbated or persists post stroke. 6) Reversible causes of UI may be present in the post-stroke period, such as medications, fecal impaction, and delirium.

An additional type of voiding dysfunction, detrusor-sphincter dyssynergia, was not described above. When the detrusor muscle is hyperactive due to a loss of cortical inhibition of urination, voiding is usually complete. After stroke, however, detrusor muscle contraction may not always coincide with coordinated relaxation of the urethral sphincters. Detrusor-sphincter dyssynergia describes the detrusor contracting against closed urethral sphincters (Gelber et al., 1993). The intra-bladder pressure rises significantly when this occurs, which may lead to reflex bladder emptying (either complete or incomplete) to avoid tissue damage (Chou et al., 2013).

Few studies have used urodynamic studies to evaluate the prevalence of these different mechanisms of UI post stroke. In a urodynamic study of 19 patients with post-stroke UI, Gelber et al. (1993) found that 37% of patients had bladder hyperreflexia, 37% had normal bladder function but incontinence indirectly caused by stroke, and 21% had bladder hyporeflexia, either due to medications or pre-existing conditions; detrusor-sphincter dyssyngergia occurred in 5% of patients. In a more recent urodynamic study of 15 patients after cerebellar stroke, Chou et al. (2013) identified detrusor overactivity in 53.5% of patients, normal detrusor function in 20% of patients, and detrusor hyporeflexia in 26.7% of patients. In addition, this study found much higher rates of detrusor-sphincter dyssynergia, occurring in 40% of studied patients, suggesting that cerebellar function may be important to ensure coordination of sphincter relaxation. Identifying the pathophysiology leading to UI post stroke has significant clinical implications, as the management of these conditions varies. For instance, some patients with detrusor hyperreflexia due to damaged cortical inhibition of urination may be continent with conservative measures such as timed voiding (Gelber et al., 1993).

Detrusor Hyperreflexia
Gelber et al. (1993), Chou et al. (2013), and Mehdi et al. (2013) identified detrusor muscle hyperreflexia or overactivity as a common cause of post-stroke UI. When a stroke affects cortical

or subcortical structures responsible for controlling the pontine micturition centre, signals from the bladder can trigger the reflexes that contract the detrusor muscle and relax the urethral sphincters. In this setting, bladder filling, even at volumes much lower than would cause urgency to void in a normal bladder, leads to contraction of the detrusor muscle and the flow of urine (Borrie, 1998). The detrusor contracts with little or no warning: the sensation or urgency to void may happen only seconds before or as voiding occurs. Hence, patients often present with urgency to void accompanying their incontinence, and voiding that is more frequent because the bladder empties at smaller volumes. These patients are more likely to have strokes that affect the anterior circulation, specifically the frontal lobe and pre-frontal cortex (Mehdi et al., 2013).

Urinary Retention
While it is the most common pattern of voiding dysfunction identified in post-stroke urodynamic studies, detrusor hyperreflexia is not inevitable after a stroke. Acute urinary retention due to inactivity or hyporeflexia of the detrusor muscle is commonly seen in the first 72 hours post stroke (Chou et al., 2013). After the first 72 hours, urinary retention is less common; in patients who experience it, other mechanisms for urinary retention predominate (Chou et al., 2013). Specifically, detrusor-sphincter dyssynergia leads to urinary retention and incomplete bladder emptying (Fader & Craggs, 2003; Nazarko, 2003). By the time patients enter stroke rehabilitation, Gelber et al. (1993) found detrusor-sphincter dyssyngergia occurred in 5% of patients who were, on average, 20 days post stroke. The prevalence of urinary retention has been reported in 21% to 47% of adults with stroke (Burney et al., 1996; Doshi et al., 2003).

Incomplete bladder emptying leads to residual urine remaining in the bladder and is a significant risk factor for the development of infections in the urinary tract (Fader & Craggs, 2003; Kim et al., 2012). It is therefore important to determine if complete bladder emptying is occurring to identify and treat the problem by evaluating the post-void residual (PVR) urine volume. Intermittent or in-and-out catheterization is considered the gold standard measure for determining PVR volume. However, portable bladder ultrasound devices are an alternative PVR measurement tool that is practical, non-invasive, and cost-effective (Chan, 1993). These devices can also be used to detect urinary retention in patients who have not voided by measuring the volume of the bladder.

There is no consensus regarding what volume of residual urine is considered abnormal (Grosshans et al., 1993). In general, two consecutive PVR volumes >150 mL indicates incomplete bladder emptying that may warrant further management (Borrie, 1998). Patients with bladder volumes >500 mL are usually considered to be in urinary retention, and often require in-and-out catheterization or other management to prevent negative sequelae associated with urinary retention if they are unable to void spontaneously (Chou et al., 2013). One study evaluated the effectiveness of a standardized bladder scan regimen using portable ultrasound devices to measure PVR in 52 patients with subacute stroke and known PVR >100 mL (Kim et al., 2012). The study used two separate protocols, one for patients with urinary retention who could not urinary volitionally, and one for patients who could do so. Overall, the standardized scan protocol was effective for managing urinary retention post stroke but did not demonstrate a reduction in other consequences during admission.

Urinary Tract Infection
Urinary tract infections (UTI) are the single most common medical complication in with stroke rehabilitation, affecting 13.6-44% of patients (Dromerick & Reding, 1994; Hung et al., 2005; Roth et al., 2001). Risk factors for UTI post stroke include age over 65 years, female sex, anterior circulation stroke, prior stroke, antidepressant use, pre-morbid UI, indwelling urinary catheter, and a post-void residual volume ≥ 100 mL (Dromerick & Edwards, 2003; Ifejika-Jones et al., 2013; Kim et al., 2012; Sabanathan et al., 1985). Voiding dysfunction is thought to contribute significantly to the risk of developing a UTI, which has the potential for adverse patient outcomes

(Kim et al., 2012). Ifejika-Jones et al. (2013) examined the impact of hospital-acquired symptomatic UTIs in patients post stroke and how symptomatic UTI affected discharge disposition. Symptomatic UTI was an independent predictor of discharge destination: patients with symptoms of UTI were 57% less likely to be discharged home and 38% less likely to be discharged to inpatient stroke rehabilitation compared to long-term care or skilled nursing facilities (Ifejika-Jones et al., 2013).

Other Factors
Incontinence may not be due to the direct neurologic consequences of stroke. Motor, cognitive, and language deficits as well as immobility and dependency are all factors that may lead to incontinence, even in patients with normal bladders (Fader & Craggs, 2003; Gelber et al., 1993; Linsenmeyer, 2012; Nazarko, 2003). Mobility impairments, such as hemiplegia or cerebellar dysfunction, may prevent patients from ambulating independently and thus rely on caregivers to assist them to the bathroom or commode. Depending on the setting and availability of caregivers, patients may not be assisted in time to avoid incontinence. Moreover, language deficits, delirium, or depression may prevent patients from communicating voiding needs to others. Medications used for secondary stroke prevention or management of other comorbidities, such as diuretics for hypertension and sodium-glucose transport inhibitors for diabetes, can increase urinary output and frequency. As well, anticholinergic medications may increase confusion or lead to urinary retention.

Conclusions Regarding Pathophysiology of Urinary Incontinence Post Stroke

- Urinary incontinence post stroke can be related to a variety of direct (i.e. damaged neuromicturition pathways) and indirect (i.e. motor, cognitive, and language deficits) factors.

17.2.3 Diagnosis and Management of Urinary Incontinence Post Stroke

Diagnosis of Urinary Incontinence
The presence of urinary incontinence (UI) is common, and although most patients will have resolution of UI by 6 months post stroke, many patients will continue to experience UI (Gelber et al., 1993; Mehdi et al., 2013). Diagnosis and management of UI is crucial in patients who have persistent UI or in patients for whom UI is causing reduced health-related quality of life, excessive caregiver burden, or impeding their progress in rehabilitation. In a set of evidence-based guidelines for stroke rehabilitation, Duncan et al. (2005) found that there was insufficient evidence to recommend for or against the use of urodynamic studies for the diagnosis of the type of UI post stroke. In a Cochrane review of UI not limited to post-stroke patients, Clement et al. (2015) developed the same conclusion, finding that urodynamics may change clinical decision-making but there was not enough evidence to support its universal use. Therefore, diagnosis of UI should be made using history and physical examination; additional investigations, including urodynamic studies, can be pursued to guide diagnosis and management when needed.

Table 17.2.3.1 outlines a very basic approach to the features suggestive of different UI types, and the subsequent section examines treatment options (Borrie, 1998).

Table 17.2.3.1 Diagnosis of Bladder Dysfunction

Features on Voiding History	Physical Examination	Post-Void Residual Volumes	Pathophysiology on Urodynamic Studies
Urge: sudden urge to void with or without incontinence	Signs of central or peripheral neurologic disease, such as stroke or multiple sclerosis	Low	Detrusor hyperactivity
Stress: unexpected voiding of small volumes with change in position or with increased intraabdominal pressure (cough, laugh, sneeze)	Incontinence is reproducible with maneuvers that increase pressure on the bladder, such as coughing	Low	Stress incontinence
Overflow: urinary retention, including difficulty initiating urination and/or emptying bladder; dribbling urine	- Palpable bladder (large volume) - Outflow obstruction: enlarged prostate, urethral stricture, or heightened sphincter tone - Reduced anal sphincter tone with or without reduced anal sensation	High	Detrusor hyporeflexia with or without detrusor-sphincter dyssynergia Outlet obstruction possible
Mixed: features of urge and stress incontinence	Variable	Variable	Mixed
Functional: unable to perform tasks that would promote continence, such as ambulating to bathroom, dexterity to remove clothes, or ability to ask for help	- Impaired mobility, language, or cognitive status - Environmental factors	Low	Bladder function may be normal
Iatrogenic	- Medications that may contribute to increased urinary output, frequency, or inability to void - Restraints that limit patient function	Variable	Bladder function may be normal

Adapted from Borrie et al. (1998)

Management of Urinary Incontinence
Given the high frequency of these two types of voiding dysfunction, clinicians must address and manage complications related to overactive bladder, incontinence, and retention in their patients post stroke (Linsenmeyer, 2012; McKenzie & Badlani, 2012; Mehdi et al., 2013).

Few high-quality studies have evaluated treatment options for UI in the post-stroke population, although many studies exist in other patient populations with UI. In the absence of robust research and evidence-based guidelines, management usually falls to clinical expertise of the treating medical team and is guided by the patient's type of incontinence. Borrie (1998) proposed that a stepwise approach is best: starting with behavioural intervention, progressing to medication if needed, and considering surgical interventions only as a last resort.

Dumoulin et al. (2005) conducted a systematic review investigating the benefits of behavioural therapies used to treat UI. The study included four RCTs, one cohort study, and recommendations from three clinical practice guidelines. There was limited evidence that using the combination of bladder retraining, urge suppression, and pelvic floor exercises reduced UI in male patients post

stroke. The authors concluded that despite increasing recognition of the benefits of behavioral approaches as treatment for stroke patients with a high occurrence of continual UI, the evidence was very limited for specific treatments.

A Cochrane review investigating optimal methods for prevention and treatment of UI post stroke in adults evaluated results from 724 patients in 12 trials (Thomas et al., 2008). There was a wide range of interventions: behavioural interventions such as timed voiding; specialized professional input interventions such as continence nurse practitioner care; complementary and alternative medicine interventions including acupuncture and moxibustion; pharmacotherapy with estrogen, oxybutynin, meclofenoxate; and physical therapy such as pelvic floor muscle training and sensory-motor feedback combined with timed voiding. The findings were tempered by small sample sizes and suboptimal study methodology across the studies. As well, a pooled analysis across all interventions was not performed.

Two trials included in the review (Brittain et al., 2000; Wikander et al., 1998) offered some evidence supporting input from specialized professionals using systematic methods to help evaluate, manage, and improve outcome of patients with continence complications. Their findings demonstrated short- and long-term improvements in UI symptoms could be established through this specialized care. Limited evidence suggested that the acute stage of rehabilitation has the largest impact on UI post stroke. However, there was a paucity of evidence from all intervention studies for UI post stroke, and so the authors concluded that further research is required.

Fluid Intake
Borrie (1998) suggested that patients' total measurable fluid intake should be approximately 1500-1800 mL per 24 hours for patients with UI post stroke. Fluid restriction is a common method of controlling urinary symptoms, including for patients with obstructive uropathy such as benign prostatic hypertrophy. However, there are no specific studies demonstrating the safety or efficacy of this technique in post-stroke UI. Care providers should be mindful that the use of intravenous fluids or a feeding tube may result in fluid loads greater than 2 L per day, which will in turn compromise bladder continence by increasing urine output (Borrie, 1998). A careful clinical assessment should be completed to ensure fluid restriction aimed at improving UI does not compromise adequate hydration.

Catheterization
Urinary catheter insertion is common in the first 48 hours of admission following stroke for indications including UI, urinary retention, and management of fluid balance (Duncan et al., 2005; Gresham et al., 1995; Wu et al., 2013). In a study of the prevalence of indwelling urinary catheters (IUC) in 2803 patients with acute stroke, Wu et al. (2013) found that 25% of had indwelling catheters placed at the time of admission. IUC use was more likely in patients with intracerebral hemorrhage than in patients with ischemic stroke, occuring in 60% and 16% respectively. Cowey et al. (2012) identified clinical indicators (e.g. urinary retention) as the main reasons for catheterization, although there was a lack of standardized consensus regarding the decision process. As well, there has been limited research regarding IUC removal post stroke, suggesting that time of day and bladder reconditioning do not impact or improve subsequent urinary incontinence (Gross et al., 2007; Moon et al., 2012).

Stroke guidelines suggest removing IUC within 48 hours to reduce adverse events and poor outcomes such as UTI (Duncan et al., 2005; Nazarko, 2003). Using the Taiwan Stroke Registry, Wu et al. (2013) found that patients with IUC for ≥3 months were more likely to experience mortality, UTI, and any complication, as well as require ventilator use (p<0.001), regardless of their stroke type. These patients were also more likley to be older in age and to have more severe stroke, suggesting that long-term IUC may be associated with poorer recovery and prognosis.

Given that approximately 40% of patients regain continence during the first two weeks post stroke, judicious use of IUCs should be standard of practice (Brocklehurst et al., 1985; Wu et al., 2013).

As an alternative to IUC use, clean intermittent catheterization has been shown to safely manage urinary retention (Bennett & Diokno, 1984; Maynard & Diokno, 1984; Webb et al., 1990). Intermittent catheterization can be utilized when a patient is unable to pass urine and/or has a substantial amount of residual urine still in the bladder. To reduce the incidence of nosocomial UTIs, the use of silver alloy-coated urinary catheters has been recommended (Duncan et al., 2005). While the cost of these catheters is greater, they may be more cost-effective considering the reductions in cost associated with treating bacterial UTIs. However, the literature upon which this recommendation was based was not specific to stroke patients.

Bladder Training
Scheduled voiding programs follow a set schedule of voiding every 2-4 hours, regardless of whether the patient has a sensation that they need to void. Timed voiding can be useful for the management of multiple types of voiding dysfunction. For patients whose cortical control of voiding is impaired and who experience urgency due to detrusor hyperreflexia, timed urination reduces the chance that the bladder fills to the point that triggers reflexic bladder emptying. In patients whose awareness of bladder fullness is reduced, following a schedule of voiding prevents unexpected voids in much the same way, by pre-emptively emptying the bladder (Borrie, 1998). Initiation of toileting in response to urgency, while shown to promote continence, often does not provide enough time to void especially when mobility is limited. Gradually, bladder training may allow for lengthening of the voiding interval as the patient becomes consistently dry (Borrie, 1998; Burgio & Burgio, 1986).

Some research had supported the use of pelvic floor muscle training in patients with stroke-related UI. When compared to standard care, this training has shown improvements in pelvic floor muscle control and reductions in UI symptoms (Engberg et al., 2002; McDowell et al., 1999; Shin et al., 2016; Tibaek et al., 2005). However, there were conflicting findings regarding its impact on quality of life (Shin et al., 2016; Tibaek et al., 2007; Tibaek et al., 2004). In a set of evidence-based stroke rehabilitation guidelines, Duncan et al. (2005) recommended the use of prompted voiding in stroke patients with UI. Similar conclusions favouring prompted voiding were drawn in a Cochrane systematic review of 355 elderly persons with UI, although stroke was not a criteria and the benefit was mild. The guidelines recommended developing and implementing individualized bladder training programs. However, a feasibility study by Thomas et al. (2014) found that not all institutions would be able to smoothly integrate such a systematic voiding program.

Pharmacological Treatments
Although UI is common after stroke, few studies have evaluated pharmacotherapy options for UI post stroke. In the aforementioned Cochrane review, Thomas et al. (2008) found that there was insufficient evidence to determine the optimal pharmacological treatment in this population. Borrie (1998) suggested that drug therapy should be implemented only after an adequate trial of behavioural interventions because they often have significant side-effects, particularly in the elderly.

Anticholinergic medications act by inhibiting detrusor contraction, and are frequently prescribed to patients with symptoms of overactive bladder or detrusor hyperreflexia (Borrie, 1998). Flavoxate is a non-specific anticholinergic, anti-muscarinic compound that has antispasmodic properties and is said to have lower anticholinergic side effects. However, its non-selective anti-muscarinic effects can produce gastrointestinal symptoms including nausea by exerting antispasmodic action on the gut. Poor compliance with flavoxate has been noted, due to lack of efficacy in reducing UI symptoms (DeMaagd & Davenport, 2012). Oxybutynin is another non-

selective anticholinergic which is frequently used, but showed no benefit over timed voiding in a small RCT (Thomas et al., 2008). Propantheline is postulated to not cross the blood-brain barrier, which offers a theoretical advantage over other non-selective anticholinergic drugs that can lead to confusion or precipitate delirium (Borrie, 1998). Tolterodine is another non-selective anticholinergic, which is thought to have less influence on salivary gland function and thus less likely to lead to dry mouth as a complication. One RCT demonstrated no benefit with tolterodine over timed voiding (Thomas et al., 2008).

Newer, more selective anticholinergic agents have been shown to effectively treat UI in populations other than stroke (Basra & Kelleher, 2008; DeMaagd & Davenport, 2012). Solifenacin is an anti-muscarinic medication that selectively inhibits the M3 muscarinic receptor, which is thought to be the primary mediator of bladder contractility (Basra & Kelleher, 2008). Its efficacy and tolerability in patients with detrusor hyperreflexia has been demonstrated in RCTs, including one trial demonstrating superiority over tolterodine, although none of these studies were specific to stroke patients with these symptoms (Basra & Kelleher, 2008). Although this medication is more specific to the bladder, it still has side effects of dry mouth and constipation which may limit its use.

Mirabegron is a first-in-class medication that prevents detrusor contraction by inhibiting beta-3-adrenergic receptors (Sacco & Bientinesi, 2012). This novel mechanism of action produces fewer anticholinergic side effects, such as dry mouth and blurred vision, and is thought to be less likely to precipitate delirium and confusion. Mirabegron has shown benefit for reducing the number of urinary episodes and the number of incontinence episodes in a systematic review of over 10,000 patients with UUI (Sacco & Bientinesi, 2012). However, this medication has not specifically been evaluated in the post-stroke population, and there is a risk of exacerbating hypertension, which may negatively impact secondary stroke prevention efforts.

Supplemental estrogen therapy is effective for post-menopausal women with UUI (Cody et al., 2009). However, oral estrogen supplementation is relatively contraindicated in patients with a history of stroke due to the strong association between supplemental estrogen and stroke and venous thromboembolism (Wassertheil-Smoller et al., 2003). Estrogen delivered via vaginal suppository results in lower systemic doses with comparable benefits for UUI (Cody et al., 2009), but should still be used with caution in patients who have had a stroke (Obstetricians & Gynecologists, 2013). For patients with overflow incontinence or detrusor hyporeflexia, bethanecol may be effective. Bethanecol is a muscarinic agonist that improves detrusor muscle contractility, which may aid bladder emptying either on its own or as an adjunct to in-and-out or intermittent catheterization (Borrie, 1998; Sonda et al., 1979).

Pharmacotherapy for UI post stroke should be evaluated for effect after initiation. Medications that are not providing measurable benefit—subjective improvement, such as less urgency, or objective improvement, such as decreased post-void residual volumes—should be discontinued. Medications providing benefit should be titrated to optimal effect, bearing in mind medication tolerability.

Table 17.2.3.2 Summary of RCTs Evaluating Non-Pharmacologic Treatment of UI Post Stroke

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Pelvic floor training		

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Pelvic floor training		
Tibaek et al. (2017) RCT (7) N$_{start}$=31 (males only) N$_{end}$=30 (males only)	E: Pelvic floor training C: Standard rehabilitation Duration: 60min sessions, 1x/wk for 12wk	• Danish prostatic symptom score (-) • Voiding diary (-) • Digital anal palpation (-)
Shin et al. (2016) RCT (6) N$_{start}$=31 (female only) N$_{end}$=27 (female only) TPS=Subacute	E: Standard Rehabilitation + Pelvic floor training C: Standard rehabilitation Duration: 50min/d, 3d/wk for 6wk (standard rehabilitation) + 50min/d, 3d/wk for 6wk (pelvic floor training)	• Maximal vaginal squeeze pressure (+exp) • Pelvic floor muscle activity (+exp) Bristol Female Urinary Tract Symptom Questionnaire (+exp)
Tibaek et al. (2006) RCT (7) Follow up to Tibaek et al. 2004 N$_{start}$=24 (females only) N$_{end}$=24 (females only) TPS=Chronic	E: Pelvic floor training C: Standard rehabilitation Duration: 30min/d, 7d/wk for 12wk	• 36-Item Short Form Health Survey (-) • Incontinence Impact Questionnaire (-)
Tibaek et al. (2005) RCT (6) N$_{start}$=24 (females only) N$_{end}$=24 (females only) TPS=Chronic	E: Pelvic floor training C: Standard rehabilitation Duration: 30min/d, 7d/wk for 12wk	• Daytime Voiding Frequency (+exp) • 24hr Pad Test (+exp) • Dynamic Endurance of Pelvic Floor Muscle (+exp) • Static Endurance of Pelvic Floor Muscle (+exp) • Contraction of Pelvic Floor Muscle (+exp)
Tibaek et al. (2004) RCT (7) N$_{start}$=26 (female only) N$_{end}$=24 (female only) TPS=Chronic	E: Pelvic floor training C: Standard rehabilitation Duration: 30min/d, 7d/wk for 12wk	• 24hr pad test (+exp) • Daytime voiding frequency (+exp) • Pelvic floor strength, endurance, function (+exp) • Incontinence Impact Questionnaire (-) • 36-Item Short Form Health Survey (-)
Engberg et al. (2002) RCT (6) N$_{start}$=19 N$_{end}$=19 TPS=Chronic	E: Pelvic floor training C: Attention control Duration: 8wk	• Continence (+exp) • Older American Research and Service Physical and Instrumental Activities of Daily Living Scale (+exp) • Folstein Mini Mental State Examination (+exp) • Clock Drawing Test (+exp) • Geriatric Depression Scale(+exp) • Performance-Based Toileting Assessment (+exp)
McDowell et al. (1999) RCT (5) N$_{start}$=105	E: Pelvic floor training C: Attention control Duration: 45min/d, 5d/wk for 3wk	• Continence (+exp) • OARS Physical and Instrumental Activities of Daily Living (-)

		• Folstein Mini-Mental State Examination Score (-) • Clock Drawing Test (-) • Geriatric Depression Scale (-)
Traditional Chinese Medicines		
Gao et al. (2012) RCT (8) N_{start}=240 N_{end}=236 TPS=Acute	E: Series of traditional Chinese herbal medicines C: Single traditional Chinese herbal medicine Duration: *Not Reported*	Activity of daily living function: • National Institutes of Health Stroke Scale (-) • Barthel Index at follow-up (-) Common symptoms post-stroke: • Difficulty in talking (+exp) • Memory loss (+exp) • Abnormal defecation (+exp) • Paruria (+exp) • Night sweating (+con) • Dysdipsia (+con)
Yun et al. (2007) RCT (6) N_{start}=41 N_{end}=39 TPS=Acute	E: Moxibustion therapy C: No therapy Duration: Direct moxibustion on 3 *qi* points 5x/d, for 10d	• International Prostate Symptoms Score (+exp) • Barthel Index (-)
Catheter usage		
Moon et al. (2012) RCT (4) N_{start}=64 N_{end}=60 TPS=Subacute	E1: Indwelling uretheral catheter removal E2: Catheter removal with 1-day clamping E3: Catheter removal with 3-day clamping Duration: 4hr/d (continual) for 1d OR for 3d	• Time to first void (-) • Volume on first void (-) • Voiding method (-) • Residual urine volume (-)
Gross et al. (2007) RCT (6) N_{start}=45 N_{Eend}=45 TPS=Subacute	E1: Catheter removal at 10:00pm of the same day order for removal was written E2: Catheter removal at 7:00am of the day after the order for removal was written	• Time to void (-) • Volume on first void (-) • Post-void residual (-) • Number of subjects requiring re-catherization (-)
Transcutaneous electrical nerve stimulation		
Liu et al. (2016) RCT (7) N_{start}=81 N_{end}=73 TPS=NR	E1: 20Hz transcutaneous electrical nerve stimulation E2: 75Hz transcutaneous electrical nerve stimulation C: No treatment Duration: 30min/d, 5d/wk for 12wk	E1 vs E2/C • Overactive Bladder Symptom Scores: (+exp_1) • Voiding diary parameters: (+exp_1) • Urodynamic values: (+exp_1) • Barthel Index: (+exp_1) E2 vs C • Overactive Bladder Symptom Scores: (+exp_2) • Voiding diary parameters: (+exp_2) • Urodynamic values: (+exp_2) • Barthel Index: (+exp_2)
Individualized rehabilitation programs		
Wikander et al. (1998) RCT (4) N_{start}=34 N_{end}=34 TPS=NR	E: Individualized rehabilitation program based on FIM scores C: Bobath-based rehabilitation program	• Continence (+exp) • Psychological Wellbeing Index (+exp) Katz Index of Independence in ADL (+exp)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp_2 indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group

+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Discussion

A number of behavioural and complementary/alternative treatment options have been studied for post-stroke UI. In general, there is a paucity of available literature for any one of these treatments, and the variable methodology may limit widespread use. Furthermore, the pre-stroke continence status, small sample sizes, and heterogeneity of the treatments and outcomes assessed limit the generalizability of the findings.

Studies evaluating the use of pharmacologic treatments, such as anticholinergics and beta-3 adrenergic agonists, are lacking in the post-stroke population. However, many of these agents have been studied in non-stroke patients with UI and have shown to be of benefit, particularly solifenacin and mirabegron. Estrogens should be used with caution, given their association with venous thromboembolism and stroke. Further research is needed to determine optimal therapies as well as the safety and efficacy of these medications, which may have significant adverse effects in the stroke population.

Conclusions Regarding the Diagnosis and Management of Urinary Incontinence

LoE	PICO statement	Number of RCTs	References
1a	**Pelvic floor training** may improve muscle control and reduce urinary incontinence when compared to **standard care or attentional control programs** especially in female participants.	7	Tibaek et al. 2017; Shin et al. 2016; Tibaek et al. 2006; Tibaek et al. 2005; Tibaek et al. 2004; Engberg et al. 2002; McDowell et al. 1999
1a	There is conflicting evidence for the effect of **pelvic floor training** on improving health-related quality of life and activities of daily living when compared to **standard care or attentional control programs.**	5	Tibaek et al. 2006; Tibaek et al. 2005; Tibaek et al. 2004; Engberg et al. 2002; McDowell et al. 1999
1b	**Traditional Chinese medicines** (e.g. herbal-based, moxibustion therapy) may not improve measures of stroke severity or activities of daily living when administered in **multiple doses** or compared to **no therapy**.	2	Gao et al. 2012; Yun et al. 2007
1b	**Traditional Chinese medicines** (e.g. herbal-based, moxibustion therapy) may improve symptoms of paruria and urinary tract function when administered in **multiple doses** or compared to **no therapy**.	2	Gao et al. 2012; Yun et al. 2007
1b	**Time or delay of catheter removal** may not improve management of urinary incontinence.	2	Moon et al. 2012; Gross et al. 2007
1b	**Transcutaneous electrical nerve stimulation** at a frequency of 20Hz or 75Hz may improve management of urinary incontinence and activities of daily living when compared to **no treatment**.	1	Liu et al. 2016
1b	**Individualized rehabilitation programs** may improve management of urinary incontinence, psychological well-being and activities of daily living when compared to a **Bobath concept approach**.	1	Wikander et al. 1998

- Diagnosis of urinary incontinence post stroke should be made based on clinical history and physical examination. Additional investigations such urodynamic studies can be pursued to guide diagnosis when needed.

- Pelvic floor training may be an effective intervention for urinary incontinence post stroke.

- Despite several pharmacological interventions for urinary incontinence, namely anticholinergic medications, there is no evidence of their effectiveness in a stroke-specific population.

- Further research is required for the effectiveness of complementary/alternative therapies as well as electromechanical devices in treating urinary incontinence post stroke.

- Catheterization is an effective intervention for urinary incontinence post stroke, but chronic catheter use is associated with adverse events and poor outcomes.

- Further research is required to examine processes to optimize catheter removal, such as bladder reconditioning.

17.3 Bowel Dysfunction Post Stroke

Bowel dysfunction is a common problem following stroke, particularly fecal incontinence and constipation. The reported prevalence of some form of fecal incontinence post stroke ranges from 7% to 56%; most patients experience resolution of fecal incontinence within 2 weeks (Brocklehurst et al., 1985). Kovindha et al. (2009) reported that incontinence of bowel and bladder (double incontinence) occurred in 33% of patients at admission to a rehabilitation unit and persisted in 15.1% at discharge. As well, Brittain et al. (2006) reported that major fecal incontinence was 4.5-times more prevalent among patients post stroke compared with controls. A variety of risk factors for fecal incontinence have been identified including stroke location, stroke severity, and functional limitations. Total anterior infarction has been identified as an independent predictor of the presence of fecal incontinence (Barrett, 2002). Harari et al. (2003) found that problems with toilet access and constipating drugs were modifiable risk factors post stroke. The authors also found that the most powerful predictor of fecal incontinence in the first few days post stroke was the initial level of consciousness and stroke severity.

Constipation post stroke has not been well studied. The prevalence is unclear, likely due to high variability in the diagnostic criteria for constipation in stroke research. Harari et al. (2004) reported that 66% of patients screened for their interventional study suffered from constipation. A similar percentage of affected patients (66%) was reported by Robain et al. (2002) among patients in stroke rehabilitation. In general, constipation is thought to be a consequence of poor fluid intake, use of constipation-inducing medications, poor dietary fiber intake, decreased mobility, and increased dependence, rather than as a direct effect of stroke (Winge et al., 2003). Mild cases can be treated by correcting some of these abnormalities, such as ensuring adequate hydration, and with interventions, such as stool softeners or pro-kinetic agents.

17.3.1 Treatment of Fecal Incontinence and Constipation Post Stroke
The management of both fecal incontinence and constipation has not been well studied in the stroke population. In terms of constipation, a multidisciplinary approach to diagnosis and treatment is warranted. An effective intervention strategy recognizes the importance of fiber and fluid intake, bowel habits, and use of medications (Winge et al., 2003). Bulk-forming laxatives, bisacodyl suppositories, stool softeners, osmotic agents, and/or stimulant laxatives may be indicated or contra-indicated depending on the needs of the individual patient. If a patient has a

fecal impaction, treatment with enemas or digital evacuation may be required (Winge et al., 2003). Only four RCTs have evaluated treatment strategies for constipation and fecal incontinence post stroke (Table 17.3.1.1).

Table 17.3.1.1 Summary of RCTs Evaluating Treatment of Fecal Incontinence and Constipation

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Suppository use		
Venn et al. (1992) RCT (3) N$_{start}$=58 N$_{end}$=51 TPS=Chronic	E1: Morning bowel training with mandatory suppository E2: Morning bowel training with optional suppository E3: Evening bowel training with mandatory suppository E4: Evening bowel training with optional suppository Duration: 30min/d, 7d/wk for 4wk + bisacodyl suppository until patient defecates for 5 consecutive scheduled times	E1/E2 vs E3/E4: • Bowel movement patterns (+exp$_1$, +exp$_2$) E1/E3 vs E2/E4: • Suppository use (-)
Meridian acupressure		
Jiang (2016) RCT (6) N$_{start}$=70 N$_{end}$=66 TPS=Chronic	E: Tui-pushing on large intestine meridian + Point sticking at Tianshu C: Routine care Duration: 20min (tui-pushing) + point sticking (at tianshu), 5d/wk for 4wk	• Constipation incidence (+exp) • First defecation time (+exp)
Traditional Japanese medicine		
Numata et al. (2014) RCT (7) N$_{start}$=34 N$_{end}$=31 TPS=Chronic	E: Diakenchuto (DKT) C: Routine care Duration: 5.0g of DKT (3x/d), 7d/wk for 4wk	• Constipation Scoring System (+exp)
Clinician follow-up		
Harari et al. (2004) RCT (6) N$_{start}$=146 N$_{end}$=133 TPS=Chronic	E: One-time nursing assessment followed by patient/carer education C: Routine care Duration: *Not Reported*	• Normal bowel movements (+exp) • Number of bowel movements (+exp) • Episodes of fecal incontinence (+exp)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Discussion

Treatment for constipation commonly involves drug therapy (i.e. use of laxatives or stimulant purgatives), and these methods are considered to be the primary means of reducing gastrointestinal discomfort for chronic constipation (Numata et al., 2014). There is a paucity of research on bowel dysfunction within a stroke population; treatment options for constipation or fecal incontinence are therefore based on usual practice (Harari et al., 2004).

In an early trial, Venn et al. (1992) found that bowel training protocols implemented under a mandatory, timed suppository use schedule did not result in in improved outcomes. However, patients in a morning bowel training group had more efficient bowel movements than those receiving training in the evening. The authors noted that efficiency of bowel regimens was greatest for patients who were assigned to a bowel training group time that coincided with their previous patterns.

Harari et al. (2004) examined effects of a nurse-led intervention that consisted of a generic education booklet for the patient and carer, a diagnostic summary, and patient-specific treatment recommendations for improved bowel functioning. Findings suggested that the intervention was associated with a significant reduction in the weekly number of uncomfortable bowel movements, and a significantly greater likelihood of making lifestyle changes helpful for bowel movement (i.e. modifications to dietary and fluid intake) compared to the routine care. These improvements were sustained at 6 months but not at 12 months. A major strength of the study was the use of an educational approach that highlighted a major benefit of structured management strategies as means for providing longer-term solutions for bowel dysfunction, instead of focusing on the pharmacological approach by increasing laxative doses.

A major limitation of conventional drug therapy for constipation is the ability of a patient to develop tolerance, and so contemporary/alternative strategies have been explored. Numata et al. (2014) evaluated a traditional Japanese medicine, Daikenchuto (DKT), for constipation post stroke. The authors found that, when administered along with conventional treatment, DKT was associated with decreased constipation as indicated by the Constipation Scoring System and a reduction in the gas volume score compared to conventional treatments alone; there were no adverse events reported. Jiang et al. (2016) examined a protocol of Tui-pushing on the large intestine meridian, along with point sticking at Tianshu, and its impact on post-stroke constipation. The protocol was associated with a significantly lower incidence of constipation and earlier time of first defecation.

Conclusions Regarding the Treatment of Fecal Incontinence and Constipation Post Stroke

LoE	PICO statement	Number of RCTs	References
2	**Morning suppository use** may improve bowel movement patterns more efficiently than **evening suppository use**.	1	Venn et al. 1992
1b	**Meridian acupressure** may lower constipation incidence and first defecation time when compared to **routine care**.	1	Jiang et al. 2016
1b	**The traditional Japanese medicine, Diakenchuto** may improve fecal incontinence when compared to **routine care**.	1	Numata et al. 2014
1b	**An additional nursing follow-up educational assessment** may improve bowel incontinence and movements when compared to **routine care**.	1	Harari et al. 2004

- Bowel dysfunction is a common complication post stroke, although it may be more directly related to non-stroke factors.

- There is limited research regarding treatments for constipation and fecal incontinence post stroke.

17.4 Venous Thromboembolism Post Stroke

17.4.1 Diagnosis of Venous Thromboembolism Post Stroke

Deep vein thrombosis (DVT) is a potentially life-threatening condition in which blood clots form in the deep veins of the body. Venous thromboembolism (VTE) occurs when these clots embolize, or break free, and travel through the body's circulatory system. VTE is life-threatening when it enters the lungs, at which point it is clinically recognized as pulmonary embolism (PE), or when it embolizes to other areas, leading to focal ischemia.

The signs and symptoms of PE are often nonspecific and can include sudden onset, pleuritic chest pain, shortness of breath, tachycardia, hypoxia, tachypnea, hemoptysis, and/or loss of consciousness (syncope). Due to its non-specific nature, diagnosis of PE often requires a high index of suspicion. This is particularly true in the stroke population, as patients may be unable to verbalize complaints due to physical and cognitive impairment. PE is often mistaken for pneumonia, which is relatively common post stroke, and can delay diagnosis or worsen patient outcomes (Kelly et al., 2001). The Wells Score is a clinical tool commonly used to identify the pre-test probability that a patient has a PE, to help guide decision-making about further testing (Table 17.4.1.1). A similar tool exists for determining the pre-test probability that a patient has a DVT (Table 17.4.1.2).

Table 17.4.1.1 Wells Scoring System for Pulmonary Embolism (Wells et al., 2000)

Criteria	Points Score
Symptoms of DVT	+3
Tachycardia (heart rate >100 beats per minute)	+1.5
Immobilization for ≥3 days OR major surgery in the previous 4 weeks	+1.5
Hemoptysis	+1
Presence of malignancy (or treatment within the last 6 months)	+1
Prior history of DVT or PE	+1.5
PE is the most likely diagnosis, or no alternative diagnosis better explains the patient's illness	+3

Sum Score for Risk of PE: Low risk 0-1 (1.3%); Moderate risk 2-6 (16.2%); High risk >6 (40.6%)

Table 17.4.1.2 Wells Scoring System for Deep Vein Thrombosis (Wells et al., 1997)

Criteria	Points Score
Paralysis, paresis, or recent orthopaedic casting of lower extremity	+1
Recently bedridden for ≥3 days or major surgery in the previous 4 weeks	+1
Localized tenderness or pain in deep vein system	+1
Swelling of entire leg	+1
Calf swelling 3 cm greater than other leg (measured 10cm below tibial tuberosity)	+1
Pitting edema greater in the symptomatic leg	+1
Collateral non-varicose superficial veins	+1
Active cancer or cancer treated within the last 6 months	+1
Alternative diagnosis is more likely than DVT	-2

Sum Score for Risk of DVT: Low risk -2-0 (3.0%); Moderate risk 1-2 (16.6%); High risk ≥3 (74.6%)

Diagnosis of Deep Vein Thrombosis

A diagnosis of DVT is made with venous Doppler ultrasound demonstrating DVT in one or more proximal leg veins, or venogram demonstrating intraluminal filling defect. DVT can be ruled out if there is a negative venogram, a negative D-dimer test, or a normal venous ultrasound in the setting of low clinical suspicion or a negative D-dimer. If the diagnosis is in doubt after a negative

venous Doppler ultrasound, the test should be repeated approximately one week later (Zierler, 2004).

Venous Doppler Ultrasound
Venous Doppler ultrasound is often used to diagnose a DVT, particularly in the deep veins of the legs. The sensitivity of the test is 95% in all patients with symptomatic proximal DVTs but falls to 73% for DVTs distal to the popliteal fossa (Zierler, 2004). Distal DVTs are considered less dangerous, as the risk of embolism from the clot is reduced compared to more proximal DVTs, although the risk may be as high as 20% as distal DVTs can extend proximally without changes in symptoms (Kelly et al., 2001; Zierler, 2004).

Venography
Venography is considered the gold standard test for DVT; it is an invasive study whereby contrast dye is injected into the leg veins and imaged with fluoroscopy, which requires radiation. Diagnosis of DVT is made if an intraluminal-filling defect is noted. Due to the wide-spread availability, lower cost, high specificity, lack of radiation exposure, and non-invasive nature of venous Doppler ultrasonography, venography has largely fallen out of favour (Zierler, 2004).

D-Dimer Assay
D-dimers are fibrin degradation products that circulate in the blood stream; fibrin is the main component of clot formation. Hypercoagulable states, conditions in which clot formation is heightened, tend to have higher circulating levels of D-dimer (Gill & Nahum, 2000). The D-dimer assay is a rapid, non-invasive and inexpensive blood test with a high negative predictive value (Gill & Nahum, 2000), meaning that negative D-dimer tests are effective for ruling out DVT (Wells et al., 2000). Positive D-dimer tests lack specificity for DVT as D-dimers are elevated in many other disease states, including cancer, congestive heart failure, and inflammatory conditions (Raimondi et al., 1993). Due to their high sensitivity, D-dimer assays have a high negative predictive value: when the D-dimer is negative, it is unlikely that the patient has a DVT. Akman et al. (2004) reported that the sensitivity and negative predictive values of the D-dimer test were high, at 95.2% and 96.2%, respectively in a group of 68 patients admitted to rehabilitation post stroke, spinal cord injury, traumatic brain injury, or hip arthroplasty. However, given that the specificity of the D-dimer is low, the positive predictive value is low as well. In the same group in inpatient rehabilitation, Akman et al. (2004) found the specificity and positive predictive value of D-dimer were 55.3% and 48.7%, respectively, for DVT.

Clinical Presentation of Pulmonary Embolism
As previously mentioned, the clinical presentation of PE is non-specific, and often a high index of suspicion is required to make the diagnosis. There is a significant range in the severity of presentation with PE: patients with a massive PE may have profound cardiovascular collapse, including hypotension, coma, and death; smaller PE with less pulmonary infarction may be associated with fever, tachycardia, tachypnea, hemoptysis, pleuritic chest pain, clinical signs of heart failure, and signs of right heart strain on ECG; subsegmental or small vessel PE may be asymptomatic (Kelly et al., 2001; Zierler, 2004). While PE is often associated with DVT, many cases are cryptogenic or have no known DVT, with only 30% having the clinical features of a DVT and only 50% demonstrating a DVT on ultrasonography (Zierler, 2004).

Ventilation-Perfusion Scanning
Ventilation-perfusion (VQ) scans are nuclear medicine tests frequently used to diagnose a PE by detecting reduced perfusion (blood flow) due to the presence of a blood clot in an area of otherwise normal, ventilated lung. The use of VQ scanning is limited in patients who are at risk of other lung abnormalities, such as pneumonia or aspiration, and therefore may not be ideal in stroke patients (Zierler, 2004).

Table 17.4.1.1 Probability of Pulmonary Embolism Based On VQ Scan Results and Clinical Suspicion

Ventilation-Perfusion Scan Results	Clinical Suspicion of Pulmonary Embolism		
	Low	Intermediate	High
High probability	56%	88%	96%
Intermediate probability	16%	28%	66%
Low probability	4%	16%	40%
Normal/near-normal probability	2%	6%	0%

Adapted from the PIOPED Investigators (Gill & Nahum 2000; PIOPED Investigators 1990)

The PIOPED investigators (1990) demonstrated that a low-probability or normal VQ scan with a low clinical suspicion of pulmonary embolism essentially excludes the diagnosis of pulmonary embolism with a negative predictive value of 96% and 98%, respectively (Gill & Nahum, 2000; PIOPED Investigators, 1990). When clinical suspicion is high and the scan indicates a high probability of pulmonary embolism, the positive predictive value is 96% (Gill & Nahum, 2000; PIOPED Investigators, 1990). General consensus is that treatment should be initiated in patients with positive VQ scans in whom there is a moderate or high index of suspicion for PE (Kelly et al., 2001; PIOPED Investigators, 1990). However, the majority of VQ scans yield non-diagnostic results, requiring further testing (PIOPED Investigators, 1990).

Pulmonary Angiography
Pulmonary angiography provides a definitive diagnosis for pulmonary embolism and is therefore considered the gold standard for diagnosis (Gill & Nahum, 2000). Pulmonary angiography directly visualizes the pulmonary vessels by percutaneous catheterization of the pulmonary arteries and injection of contrast dye into a pulmonary artery branch (Gill & Nahum, 2000). A negative pulmonary angiogram excludes clinically relevant pulmonary embolism (Gill & Nahum, 2000; Tapson et al., 1999). This invasive test poses significant risk to patients, including contrast reactions, contrast-induced kidney injury, risk of bleeding from arterial puncture, and stroke from arterial manipulation; it is also associated with a mortality rate of up to 0.5% (Newman, 1989; Stein et al., 1992). Relative contraindications include significant bleeding risk, allergy to contrast medium, and renal insufficiency (Gill & Nahum, 2000). Moreover, the test is expensive and personnel-intensive. Due to the advent of non-invasive, lower risk methods of evaluating the pulmonary arterial tree, pulmonary angiography has largely fallen out of use for the detection of PE (Zierler, 2004).

CT Pulmonary Angiography
In most secondary and tertiary care centres with CT scan capabilities, CT pulmonary angiography (CTPA) is the diagnostic test of choice in patients with suspected PE (Zierler, 2004). In a systematic review and meta-analysis of CTPA for pulmonary embolism diagnosis, Safriel & Zinn (2002) found the sensitivity to be 74.1% and the specificity to be 89.5%. CTPA has become the diagnostic method of choice; however, there is no high-level evidence to support this practice (Zierler, 2004). Technological advancements have decreased the cost and increased the sensitivity and specificity of this test (Zierler, 2004).

Conclusions Regarding the Diagnosis of Venous Thromboembolism Post Stroke

- Deep vein thrombosis is diagnosed using venous Doppler ultrasound, D-dimer assay, and/or venography.

- Pulmonary embolism is diagnosed using ventilation-perfusion scanning, CT pulmonary angiography, and/or traditional pulmonary angiography.

17.4.2 Prevalence of Venous Thromboembolism Post Stroke

DVT and PE remain a significant cause of morbidity and mortality in stroke patients undergoing rehabilitation (Desmukh et al., 1991). Patients are at highest risk of developing a DVT between the second and seventh day after stroke (Brandstater et al., 1992). The incidence of post-stroke DVT varies considerably by study, ranging from 22% to 73% (Izzo & Aquino, 1986; Landi et al., 1992; Miyamoto & Miller, 1980). Brandstater et al. (1992) reviewed 12 studies evaluating the incidence of DVT in ischemic stroke, hemorrhagic stroke, or both. The incidence of DVT ranged from 23% to 75% and, in most studies, was approximately 50% (Bornstein & Norris, 1988; Czechanowski & Heinrich, 1981; Denham et al., 1973; Dickmann et al., 1988; Gibberd et al., 1976; McCarthy & Turner, 1986; Mellbring et al., 1986; Prasad et al., 1982; Prins et al., 1989; Turpie et al., 1987; Warlow et al., 1976). In this review, the authors cited several studies that noted that DVT and PE risk continues beyond the initial two weeks post stroke and into the phase of active rehabilitation (Brandstater et al., 1992).

The prevalence of DVT among patients admitted for rehabilitation is lower than in acute care, ranging from 12 to 40%, depending on the provision of anticoagulants, mobility status, and method of detection used (Wilson & Murray, 2005). The incidence of DVT diagnosed during rehabilitation is lower still, ranging from 5% to 11% (Harvey et al., 2004). Brandstater et al. (1992) evaluated two studies of 118 patients who were screened for DVT before admission to inpatient rehabilitation post stroke. The authors reported 31% of patients admitted to rehabilitation units had a DVT, and the mean time between stroke onset and screening was 45 days (Izzo & Aquino, 1986; Sioson et al., 1988). Using venography, Cope et al. (1973) reported a DVT prevalence of 31% in patients admitted to a stroke rehabilitation centre. Miyamoto and Miller (1980) screened patients with I-125 fibrinogen, a precursor to D-dimer, an average of 9 days following admission to stroke rehabilitation and found a 29% prevalence of DVT.

VTE often begins with a distal DVT in the calf (Cogo et al., 1993; Nicolaides et al., 1971; Philbrick & Becker, 1988). Previously, distal DVTs were thought to rarely cause PEs and therefore were considered less worrisome (Kakkar et al., 1969). However, 20% of distal DVTs will go on to extend into the proximal veins, and therefore put patients at increased risk (Brandstater et al., 1992; Kakkar et al., 1969; Kelly et al., 2001). When DVT causes symptoms, over 80% of those involve the popliteal or more proximal veins (Kearon et al., 1998). Clinical findings of DVT such as leg pain, swelling, and erythema may be present in less than half of patients, even when diagnostic tests are positive (Brandstater et al., 1992). On admission to a rehabilitation center, clinical features of a DVT were present in only 5-10% of patients in whom diagnostic testing had demonstrated the presence of a DVT (Izzo & Aquino, 1986; Miyamoto & Miller, 1980; Sioson et al., 1988). Similar findings have been reported in more recent studies (Zierler, 2004).

Like DVT, the incidence of PE post stroke varies widely between studies; estimates range from 0.8% at 2 weeks (IST Group 1997) to 39% at 10 days (Dickmann et al., 1988). A review of the Registry of the Canadian Stroke Network in 2013 by the Stroke Outcomes Research Canada Working Group reported a similar incidence of PE (Pongmoragot et al., 2013). In 11,287 patients with acute ischemic stroke, PE was identified in 0.78% and was associated with greater disability at discharge (85.4% vs. 63.6%; P<0.001) as well as higher risk of death at 30 days (25.8% vs. 13.6%; P<0.001) and at 1 year (47.2% vs. 24.6%; P<0.001) (Pongmoragot et al., 2013). In the absence of DVT prophylaxis, one study found over 60% of dense hemiplegics develop DVTs and 9-15% have PE, with an associated 1-2% mortality rate (Sioson et al., 1988). Indeed, PE has been reported to be the fourth most common cause of death in the first 30 days post stroke, and the risk of VTE persists thereafter (Bounds et al., 1981).

Given the relatively high prevalence of DVT and PE post stroke, identifying patients who are at increased risk is crucial to direct clinical management. Features that increase risk of DVT include

obesity, lower limb paresis, reduced consciousness, and a history of DVT (Imberti & Prisco 2005). Gregory and Kuhlemeier (2003) found that increased length of hospital stay and hemorrhagic stroke were independent risk factors for DVT in acute care. Similarly, Skaf et al. (2005) observed an increased rate of PE, DVT, and VTE in patients with hemorrhagic stroke relative to ischemic stroke, which may reflect decreased use of DVT prophylaxis in this population due to the concerns for increased bleeding risk (Skaf et al., 2005). Using a multivariable regression model, Kelly et al. (2004) identified advanced age and a Barthel Index ≤9 as the two major risk factors for the development of DVT two days post stroke.

Conclusions Regarding the Prevalence of Venous Thromboembolism Post Stroke

- Deep vein thrombosis and pulmonary embolism are common and serious post-stroke complications.

17.4.3 Pharmacological Prevention of Venous Thromboembolism Post Stroke

Prophylactic anticoagulant therapy is widely used for preventing DVT and PE from occurring during acute hospitalization for a number of indications, including stroke. Prophylaxis is aimed at reducing the occurrence of new thrombosis episodes and requires lower doses than active treatment of a known or pre-existing thrombus. Even at lower doses, prophylactic anticoagulation can lead to serious complications related to increased risk of bleeding. To aid in clinical decision-making, the authors of the CLOTs trials attempted to develop a prediction model to identify immobile patients at higher risk of DVT (Dennis et al., 2011). While a few factors were identified as independent predictors for developing DVT – including dependency before stroke, history of DVT/PE, inability to lift arms, and diabetes – the resulting model did not discriminate well between patients who did and did not develop DVTs.

Clinical practice guidelines for prophylactic anticoagulation vary. The American College of Physicians' guideline for hospitalized, non-surgical inpatients including acute stroke recommended against universal use of VTE prophylaxis and the use of graduated compression stockings (Qaseem et al., 2011). Instead, the guidelines recommend heparin or heparinoid pharmacotherapy for VTE prophylaxis only in patients whose risk of VTE outweighs their risk of major bleeding (Qaseem et al., 2011). The European Stroke Organisation's guidelines for VTE prophylaxis after acute ischemic stroke supported the use of intermittent pneumatic compression, heparinoids, low molecular weight heparin (LMWH), and unfractionated heparin (UFH) in patients in whom clinical judgment indicates the risk of VTE outweighs the risk of intracranial/extracranial bleeding (Dennis et al., 2016). These guidelines recommended against graduated compression stockings and neuromuscular electrical stimulation, as studies of efficacy and safety were inadequate (Dennis et al., 2016).

The Canadian Best Practice Recommendations for Stroke Care stated that patients with acute stroke at high risk of VTE should be started on VTE prophylaxis immediately if there is no contraindication [Evidence Level A] (Casaubon et al., 2015; Lindsay et al., 2010):
1. LMWH should be considered for patients with acute ischemic stroke at high risk of VTE, or UFH for patients with renal failure [Evidence Level A]
2. For patients admitted to hospital and remaining immobile for >30 days, use of ongoing pharmacological VTE prophylaxis is recommended [Evidence Level C]
3. For patients with intracerebral hemorrhage, antiplatelet and anticoagulant agents may be safe and effective for DVT prophylaxis, but should be avoided for at least 48 hours after onset [Evidence Level C]

There are few studies evaluating the efficacy of DVT prophylaxis in inpatient rehabilitation post stroke. Guidelines are vague with respect to when to discontinue DVT prophylaxis after acute

stroke for patients in the rehabilitation setting. Common practice is to continue DVT prophylaxis until the patient is ambulatory or until they are discharged from the rehabilitation unit. Although clinically symptomatic DVTs are less common in the rehabilitation setting, a review of patients admitted to a stroke rehabilitation unit on average 60 days post stroke demonstrated that 11% of patients had evidence of a DVT (Oczkowski et al., 1992). The odds of having a DVT were 17.6 times greater if the patient was bedridden or wheelchair bound.

Unfractionated Heparin

Heparin acts as an anticoagulant by forming a complex with antithrombin, catalysing the inhibition of several activated blood coagulation factors: XIIa, XIa, IXa, Xa, and thrombin. UFH has an immediate onset of action and is most often used in acute conditions. It must be given parenterally, and it is typically given in intravenous or subcutaneous form. Although LMWH has become more popular in the treatment of DVT, the effects of intravenous heparin can be reversed rapidly. Bleeding is the most common adverse effect of heparin, while thrombocytopenia is an uncommon but serious side effect of the treatment (Pineo, 2004). Osteoporosis is associated with the prolonged use of high doses of heparin, although its occurrence is infrequent.

Low Molecular Weight Heparin and Heparin Analogues

LMWH is derived from standard heparin through chemical or enzymatic depolymerization. Whereas UFH has a molecular weight of 5,000 to 30,000 Daltons, LMWH has a lower molecular weight, ranging from 1,000 to 10,000 Daltons. LMWH has the same mechanism of action as UFH, but binds less strongly to protein, has enhanced bioavailability, interacts less with platelets, and yields a predictable dose response (Rydberg et al., 1999). The clinical advantages of LMWH include predictability, dose-dependent plasma levels, a long half-life, and less bleeding for a given antithrombotic effect (Rydberg et al., 1999). Thrombocytopenia is not associated with short-term use of LMWH, unlike UFH (Pineo, 2004). LMWH is administered once or twice daily, both during the high-risk period when prophylaxis for DVT is recommended and also while waiting for oral anticoagulation to take effect in the treatment of DVT. The activated partial thromboplastin time does not need to be monitored, and the dosage does not need to be adjusted (Rydberg et al., 1999).

Danaparoid sodium (Orgaran) is an alternative anticoagulant for patients who develop heparin-induced thrombocytopenia from heparin therapy (Hull & Pineo, 2004). Danaparoid is a low molecular weight heparinoid that inactivates thrombin. The major difference between danaparoid and other low molecular weight heparins is that danaparoid is devoid of heparin or heparin fragments, which are thought to cause thrombocytopenia by cross-reactivity with platelets. Its active components consist of heparin sulfate, dermatan sulfate, and chondroitin sulfate.

Table 17.4.3.1 Types of Heparinoids

Generic Name	Trade Name
Dalteparin	Fragmin
Danaparoid	Orgaran
Enoxaparin	Lovenox
Ardeparin	Normiflo
Parnaparin, Reviparin	Clivarine
Tinzaparin	Logiparin, Innohep
Certoporain	Alphaparin, Sandoparin

Warfarin (Coumadin)

Warfarin is a vitamin K antagonist that inhibits the synthesis of clotting factors II, VII, IX, and X, as well as anticoagulation proteins C and S. Therapeutic doses of warfarin reduce the production of vitamin K-dependent clotting factors by approximately 30 to 50 percent (Horton & Bushwick, 1999). The dose of warfarin is titrated to clinical effect by monitoring the International Normalized

Ratio (INR), a measure of anticoagulation effect. Clinical evidence indicates that an INR of 2.0-3.0 is sufficient for prophylaxis and treatment of VTE while minimizing the risk of hemorrhage associated with higher INRs (Horton & Bushwick, 1999). Given that warfarin inhibits the synthesis of vitamin K-dependent clotting factors, its anticoagulation effect is not present until approximately the fifth day of therapy. During this time, however, anticoagulation proteins C and S are inhibited, and the risk of clot formation is heightened. Concomitant use of heparin or heparinoid therapy, which has immediate onset of action, may be required to bridge the patient during the time it takes warfarin to have effect. Continuous anticoagulation during this period usually requires heparin therapy to overlap with warfarin therapy for 4 to 5 days for therapeutic anticoagulation if clots are already present, although there is insufficient evidence that this is required for VTE prophylaxis (Sandercock et al., 2015).

Novel Oral Anticoagulants
Novel Oral Anticoagulants (NOACs) belong to a relatively new pharmacologic medication class of factor Xa inhibitors and direct thrombin inhibitors, which may be taken orally instead of parenterally. In general, these medications offer a number of benefits over warfarin, including standardized dosing without the need for monitoring or adjustment, predictable pharmacokinetics and bioavailability, ease of dosing on an inpatient and outpatient basis, and evidence of effectiveness. Unlike warfarin, however, these medications often lack an antidote, which can be problematic for patients who develop serious bleeding. Few studies have examined the use of NOACs for VTE prophylaxis. A recent Cochrane review found insufficient evidence to recommend the use of argatroban, an oral direct thrombin inhibitor, for VTE prophylaxis post stroke (Sandercock et al., 2015). However, due to their relative convenience compared to warfarin and parenterally administered medications, the use of NOACs will likely become more widespread.

Systematic Reviews of Pharmacotherapy
A review by Andre et al. (2007) calculated the number needed to treat (NNT) to prevent one post-stroke DVT for various DVT prophylaxis methods, which is presented in Table 17.4.3.2.

Table 17.4.3.2 Number Needed to Treat for Deep Vein Thrombosis Prevention

Intervention	Number Needed to Treat (NNT)
LMWH	1-4
UFH	2-10
Warfarin	9
Compression Devices	9-16
Aspirin	> 300

Adapted from Andre et al. (2007)

In a systematic review of 11 studies with 3048 subjects, Bath et al. (2000) evaluated the safety and efficacy of LMWH, including dalteparin, danaparoid, mesoglycan, nadroparin and tinzaparin, relative to placebo. While treatment was associated with a significant reduction in the occurrence of DVT (OR 0.27, 95% CI 0.08-0.96), it was accompanied by a significant increase in the risk of extracranial hemorrhage (OR 2.17, 95% CI 1.10-4.28). The authors concluded that LMWH should not be used routinely after ischemic stroke.

A review of 16 RCTs with 23,043 subjects by Kamphuisen and Agnellu (2007) investigated the benefit/risk ratio from pharmacological prophylaxis for VTE in patients with acute ischemic stroke. The studies included had small number of events and varied in anticoagulant treatment doses. High-dose UFH was associated with decreased incidence of PE, increased intracranial hemorrhage, and increased extracranial hemorrhage compared to control. High-dose LMWH reduced the incidence of DVT and PE, but increased the risk of bleeding, comparable to high-dose UFH. Low-dose LMWH decreased DVT and PE, and was not associated with a higher rate

of hemorrhage. The authors concluded low-dose LMWH has the most favourable risk/benefit profile.

In a meta-analysis of patient-level data, Laporte et al. (2011) compared the use of UHF (5000 units subcutaneous 2-3 times daily) and enoxaparin (4000 units subcutaneous once daily) in the prevention of DVT. The analysis included the results from two trials restricted to patients with acute stroke patients (Hillbom et al., 2002; Sherman et al., 2007). Compared with UFH, enoxaparin was superior for preventing DVT and PE. Enoxaparin use was associated with risk reductions of 37% for total VTE and 62% for symptomatic VTE at day 15. There was also a slight reduced risk for mortality in patients receiving enoxaparin compared to UFH. The incidence of major bleeding episodes was similar between UFH and enoxaparin.

To clarify the safety and efficacy of anticoagulants for DVT in hemorrhagic stroke, Paciaroni et al. (2011) conducted a meta-analysis of 4 trials (2 randomized and 2 non-randomized) evaluating LMWH or UFH compared to no treatment or compression stockings. Treatment was initiated within 6 days of stroke and continued for up to 14 days; follow-up ranged from 10 days to 3 months after treatment. There was a non-significant decrease in DVT risk (RR 0.77, 95% CI 0.44-1.34) and death (RR 0.76, 95% CI 0.57-1.03) favouring the LMWH and UFH compared to no treatment or compression stockings, but these treatments had a non-significant increased risk in hematoma enlargement (RR 1.42, 95% CI 0.57-3.53).

A Cochrane review of 24 trials with 23,748 patients compared the effectiveness of various pharmacologic agents for of VTE prophylaxis post stroke (Sandercock et al., 2015), which was an update to a series of previous reviews (Gubitz et al., 2000; Gubitz et al., 2004; Sandercock et al., 2008). Based on 11 trials with 22,776 patients, there was no evidence that initiating VTE prophylaxis within 14 days of stroke reduced all-cause mortality. Earlier initiation of therapy was associated with fewer ischemic strokes, but this finding was tempered by the concurrent increase in intracranial hemorrhages. Early therapy was also associated with a reduction in the frequency of symptomatic PE, but this finding was offset by increased risk of extracranial bleeding. The use of anticoagulation for VTE prophylaxis was associated with lower rates of VTE, including ischemic stroke, PE, and DVT, but was also associated with increased intracranial and extracranial hemorrhages. The authors concluded that the data does not support routine, widespread use of anticoagulation for VTE prophylaxis post stroke.

Table 17.4.3.3 Summary of RCTs Evaluating Pharmacotherapy for the Prevention of VTE

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
LMWH vs UFH		
Sherman et al. (2007) PREVAIL RCT (7) N$_{start}$=1762 N$_{end}$=NR TPS=Acute	E: LMWH (enoxaparin) C: UFH Duration: 40mg of LMWH (subcutaneously; 1x/d) for 10d (consecutively) OR 5000U of UFH (subcutaneously; 1x every 12hr) for 10d (consecutively)	• Incidence of DVT (+exp) • Favourable outcome (+exp) • Bleeding complications (+exp) • Incidence of PE (-) • Reduction of Mortality (-)
Diener et al. (2006) PROTECT RCT (9) N$_{start}$=545	E: LMWH (certoparin) C: UFH Duration: 3000U of certoparin (1x/d) +placebo (2x/d) OR 5000U of UFH (3x/d)	• Incidence of DVT (-) • Incidence of PE (-) • Bleeding complications (-) • Reduction of Mortality (-)

N_{end}=NR TPS=Acute		
[Hillbom et al](). (2002) RCT (8) N_{start}=212 N_{end}=165 TPS=Acute	E: LMWH (enoxaparin) C: UFH Duration: 40mg of LMWH (subcutaneously; 1x/d), 7d/wk for 2wk OR 5000 IU of UFH (subcutaneously; 3x/d), 7d/wk for 2wk	• Incidence of DVT (-) • Incidence of PE (-) • Bleeding complications (-) • Reduction of Mortality (-)
[Dumas et al](). (1994) RCT (8) N_{start}=179 N_{end}=158 TPS=Acute	E: LMWH C: UFH Duration: 1250 anti-factor Xa units (subcutaneously; 1x/d), for 9d (consecutively) OR 5000 IU (subcutaneously; 2x/d) for 9d (consecutively)	• Incidence of DVT (-) • Incidence of PE (-) • Bleeding complications (-) • Reduction of Mortality (-)
[Turpie et al](). (1992) RCT (7) N_{start}=87 N_{end}= TPS=Acute	E: LMWH (danaparoid) C: UFH Duration: 750 anti-factor Xa units (subcutaneously; 2x/d) for 5000 U (subcutaneously; 2x/d)	• Incidence of DVT (+exp) • Bleeding complications (-)
LMWH vs Aspirin		
[Wu et al.]() (2014) RCT (3) N_{start}=297 N_{end}=NR TPS=Acute	E: LMWH + Aspirin + Calcium C: Aspirin Duration: 6000 IU of LMWH/Calcium (daily) + 100mg Aspirin (daily) for 10d OR 150mg Aspirin (daily) for 10d	• Bleeding complications (-) • Reduction of Mortality (-)
[Bath et al.]() (2001) TAIST RCT (7) N_{start}=1468 N_{end}=1438 TPS=Acute	E1: High-dose LMWH (tinzaparin) E2: Medium-dose LMWH (tinzaparin) E3: Aspirin Duration: 175 anti-Xa IU/kg (high-dose) daily for 10d (consecutively) OR 100 anti- Xa IU/kg (medium-dose) daily for 10d OR 300mg aspirin (daily) for 10d (consecutively)	<u>E1 vs E3</u> • Incidence of DVT: (+exp_1) • Bleeding complications: (+exp_1) <u>E2 vs E1/E3</u> • Incidence of DVT: (-) • Bleeding complications: (-) • Incidence of PE (-) • Favourable outcome (-) • Reduction of Mortality (-)
[Berge et al.]() (2000) HAEST RCT (9) N_{start}=449 N_{end}=NR TPS=Acute	E: LMWH (dalteparin) C: Aspirin Duration: 100 IU/kg (subcutaneously; 2x/d) 1x/d for 14d (consecutively) OR Aspirin (260mg) 1x/d for 14d (consecutively)	• Incidence of VTE (-) • Bleeding complications (-) • Favourable outcome (-) • Mortality (-)
LMWH vs Placebo		
[TOAST investigators]() (1998) RCT (9) N_{start}=1281 N_{end}=NR TPS=Acute	E: LMWH (danaparoid) C: Placebo Duration: 0.8 U/mL anti-factor Xa (LMWH) for 7d (consecutive) OR 0.8 U/mL placebo for 7d (consecutive)	• Incidence of DVT: 7d (-), 3mo (+exp) • Favourable outcome: 7d (+exp), 3mo (-) • Bleeding complications (+exp) • Incidence of PE (-)
[Kay et al](). (1995) RCT (7) N_{start}=312 N_{end}=NR	E1: High-dose LMWH (nadroparin) E2: Low-dose LMWH (nadroparin) C: Placebo	• Favourable outcome: 10d (-), 3mo (-), 6mo (+exp_2) • Reduction of Mortality (-)

TPS=Acute	Duration: 4100 anti-factor Xa IU (High-Dose LMWH; subcutaneously) 2x/d (every 12hr) for 10d OR 4100 anti-factor Xa IU (Low-Dose LMWH; subcutaneously) 1x/d (every 12hr alternate between low dose and placebo) for 10d OR 4100 anti-factor Xa IU (placebo; subcutaneously) 1x/d (every 12hr) for 10d Note: All patients received a dose of Aspirin (100mg) at the end of the study	
Sandset et al. (1990) RCT (8) N_{start}=103 N_{end}= TPS=Acute	E: LMWH (fragmin) C: Placebo	• Incidence of DVT (-) • Incidence of PE (-) • Bleeding complications (-) • Reduction of Mortality (-)
Prins et al. (1989) RCT (6) N_{start}=60 N_{end}=54 TPS=Acute	E: LMWH (fragmin) C: Placebo Duration: 2500 anti-Xa U (subcutaneously; 2x/d) for 14d (consecutively) OR 2500 U placebo (subcutaneously; 2x/d) for 14d (consecutively)	• Incidence of DVT (-) • Bleeding complications (-) • Reduction of Mortality (-)
Turpie et al. (1987) RCT (7) N_{start}=75 N_{end}=66 TPS=Acute	E: LMWH (danaparoid) C: Placebo Duration: 1000 anti-factor Xa units (loading dose LMWH; intravenously) followed by 750 anti-factor-Xa units (2x/d; LMWH subcutaneously) for 14d (consecutively) OR 1000 anti-factor Xa units (placebo; intravenously) followed by 750 anti-factor-Xa units (2x/d; placebp subcutaneously) for 14d	• Incidence of DVT (+exp) • Bleeding complications (-)
**UFH vs Placebo/Other**	
Pambianco et al. (1995) RCT (5) N_{start}=508 N_{end}=360 TPS=Acute	E1: LMWH E2: Neuromuscular electrical stimulation E3: Intermittent pneumatic compression C: Standard Therapy Duration: 5000 IU (3x/d), 7d/wk for 28d (LMWH) OR 30min/d, 5d/wk for 28d (NMES) OR 8hr/d (at night), 7d/wk for 28d (IPC)	• Incidence of DVT (-)
McCarthy & Turner (1986) RCT (4) N_{start}=305	E: UFH C: Placebo	• Incidence of DVT (+exp)
McCarthy et al. (1977) RCT (5) N_{start}=32 N_{end}=24 TPS=Acute	E: UFH C: Placebo Duration: 5000 U of UFH (subcutaneously; 3x/d) + 60mg of potassium iodide for 14d (consecutively) OR 60mg potassium iodide for 14d (consecutively)	• Incidence of DVT (+exp)

Discussion

Three RCTs investigated the impact of UFH on DVT post stroke. When compared to placebo, UFH was associated with a significantly lower rate of DVT in two trials (McCarthy & Turner, 1986; McCarthy et al., 1977). However, when compared to neuromuscular electrical stimulation or intermittent pneumatic compression, UFH was associated with a comparable rate of DVT (Pambianco et al., 1995).

Several RCTs were identified in which LMWH was evaluated for efficacy in reducing the rate of VTE relative to UFH, aspirin, or placebo. When compared to placebo, LMWH had similar rates of mortality (Kay et al., 1995; Prins et al., 1989; Sandset et al., 1990). Although the high-quality, multicentre TOAST trial found that LMWH was associated with a higher rate of bleeding complications that placebo (TOAST investigators, 1998), three other RCTs found similar rates between the interventions (Prins et al., 1989; Sandset et al., 1990; Turpie et al., 1987). TOAST also found that LMWH was associated with a short-term improvement in favourable outcome (TOAST investigators, 1998), but Kay et al. (1995) found significant improvements in the long term. In terms of DVT incidence, two trials of danaparoid found significantly lower rates relative to placebo, while two trials of fragmin found similar rates between interventions (Sandset et al., 1990; Turpie et al., 1987).

When compared to aspirin, the TAIST trial reported that high-dose LMWH was associated with higher rates of bleeding complications (Bath et al., 2001), although lower doses in TAIST and other trials were not associated with these complications or mortality (Bath et al., 2001; Berge et al., 2000; Wu et al., 2014). TAIST also reported that high-dose LMWH (tinzaparin) was associated with a significantly lower incidence of DVT than aspirin (Bath et al., 2001). However, the HAEST trial found that another LMWH (dalteparin) had similar rates of incident VTE relative to aspirin (Berge et al., 2000).

Similar to the aforementioned research, the evidence comparing LMWH and UFH is inconsistent. An earlier trial found that danaparoid was more effective than UFH in reducing the incidence of DVT post stroke (Turpie et al., 1992). However, a subsequent trial with more participants and of higher quality found the two interventions to be similar in efficacy and safety (Dumas et al., 1994). While the PREVAIL trial found enoxaparin to be superior to UFH in reducing the incidence of DVT and increasing the rate of favourable outcome (Sherman et al., 2007), Hillbom et al. (2002) found no significant difference between the two medications; PREVAIL found greater rates of bleeding complications with the LMWH (Sherman et al., 2007). In the PROTECT trial, certoparin and UFH demonstrated similar rates of DVT, PE, bleeding complications, and mortality (Diener et al., 2006).

Conclusions Regarding the Prevention of Venous Thromboembolism Post Stroke

LoE	PICO statement	Number of RCTs	References
1a	There is conflicting evidence whether **low molecular weight heparin** is more effective than **unfractionated heparin, aspirin, or placebo** in reducing the incidence of deep venous thrombosis and the risks of hemorrhages**.**	13	Wu et al. 2014; Sherman et al. 2007; Diener et al. 2006; Hillbom et al. 2002; Bath et al. 2001; Berge et al. 2000; TOAST investigators, 1998; Kay et al. 1995; Dumas et al. 1994; Turpie et al. 1992; Sandset et al. 1990; Prins et al. 1989; Turpie et al. 1987
2	**Unfractionated heparin** may reduce the incidence of deep venous thrombosis when compared to **placebo**.	3	Pambianco et al. 1995; McCarthy & Turner, 1986; McCarthy et al. 1977
2	**Unfractionated heparin** may not have a difference in reducing the incidence of deep venous thrombosis when compared to **pneumatic compression or neuromuscular electrical stimulation**.	1	Pambianco et al. 1995

- It is unclear whether low molecular weight heparin and unfractionated heparin are effective in preventing venous thromboembolism post stroke, without an increased risk of bleeding complications.
- However, the efficacy of these medications has been demonstrated in non-stroke populations.

17.4.4 Mechanical Devices for Prevention of Venous Thromboembolism Post Stroke

External, physical forms of DVT prophylaxis include graduated compression stockings (GCS), intermittent pneumatic compression (IPC), or neuromuscular electrical stimulation (NMES). The use of these devices is appealing because of the lower risk of bleeding, as no anticoagulation is required.

The mechanism by which GCS reduce the risk of DVT is not well understood. The stockings compress the surface veins, keeping their diameter small and forcing blood into the deep vein system, which is thought to increase blood flow in deep veins and reduce venous insufficiency (Amaragiri & Lees, 2000). A Cochrane review by Amaragiri and Lee (2000) suggested that there is a significant decrease in DVT risk among post-surgical patients who wore GCS; the review did not include an identified RCT of patients post stroke (Muir et al., 2000). While often considered a relatively benign intervention, their use was associated with serious side effects such as skin ulceration and necrosis (Amaragiri & Lees, 2000). In a later Cochrane review, Naccarato et al. (2010) examined the effectiveness of both GCS (3 RCTs, 177 patients) and IPC devices (2 RCTs, 2615 patients) post stroke. Neither device significantly reduced the risk of DVT or death. The authors concluded that there was insufficient evidence to support the use of physical methods in routine DVT prophylaxis.

In patients with contraindications to anticoagulation, or who develop VTE despite anticoagulation, invasive mechanical means of VTE prevention can be pursued. Inferior vena cava (IVC) filters are physical devices inserted percutaneously into the IVC to act as a physical barrier to the

migration of blood clots from the deep veins of the legs into the lungs. These devices are therefore primarily for PE prophylaxis, and do not prevent DVT.

IVC filters have been studied for preventing PE in a retrospective cohort study (Somarouthu et al., 2011). At baseline, 42.9% of patients enrolled in the study had a pulmonary PE on imaging prior to IVC filter placement. The most common indication for IVC filter in this study was contraindication to anticoagulation (68%). Symptomatic PE occurred in 15% of patients after IVC filter placement for an average follow-up period of 1.7 years. Although 49% of patients died, only 0.8% of patient deaths were attributed to post-IVC filter PE. The authors concluded that IVC filters had an acceptable safety profile and were effective at preventing life-threatening PE.

Table 17.4.4.1 Summary of RCTs Evaluating Mechanical Devices for the Prevention of DVT

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Intermittent pneumatic compression (IPC)		
Dennis et al. (2013) CLOTS 3 RCT (6) N$_{start}$=2876 N$_{end}$=1880 TPS=Acute	E: IPC C: Standard care Duration: 24hr/d, 7d/wk for 4wk	• Incidence of DVT (+exp) • Skin issues (+exp)
Prasad et al. (1982) RCT (5) N=26	E: IPC C: Standard care	• Incidence of DVT (-)
Graded compression stockings (GCS)		
Azami et al. (2017) RCT (6) N$_{start}$=88 N$_{end}$=88 TPS=NR	E: Thigh high GCS C: Knee high GCS Duration: 24h/d for 10d	• Prevalence of DVT (-)
Dennis et al. (2010) RCT (6) CLOTS 2 N$_{start}$=3114 N$_{end}$=NR TPS=Acute	E: Thigh-length GCS C: Below-knee GCS Duration: 24hr/d, 7d/wk for 4wk	• Incidence of DVT (+exp) • Skin Issues (+con)
Dennis et al. (2009) CLOTS 1 RCT (8) N$_{start}$=2518 N$_{end}$=NR TPS=Acute	E: Thigh-length GCS C: Standard care Duration: 24hr/d, 7d/wk for 4wk	• Incidence of DVT (-) • Skin issues (+exp)
Lacut et al. (2005) VICTORIAH RCT (7) N$_{start}$=151 N$_{end}$=119 TPS=Acute	E: Thigh-length GCS + IPC C: Thigh-length GCS Duration: 24hr/d for 10d (consecutively)	• Incidence of DVT (+exp)
Muir et al. (2000) RCT (7)	E1: Early mobilization E2: Thigh-length GCS	• Incidence of DVT (-)

N_{start}=98 N_{end}=87 TPS=Acute	C: Standard care Duration: *Not Reported Clearly*	• National Institutes of Health Stroke Scale (-) • Waterlow Score (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Discussion
The CLOTS trials were large, high-quality, multicentre RCTs that examined various interventions for the prevention of DVT post stroke. In the first trial, thigh-length GCS demonstrated similar rates of incident DVT to standard care, and were associated with notable skin issues (e.g. breaks, blisters, blisters, necrosis) (Dennis et al., 2009); these findings supported the results of a previous trial comparing GCS to standard care (Muir et al., 2000). In the second trial, thigh-length GCS demonstrated superiority to below-knee GCS in reducing the rate of DVT (Dennis et al., 2010). In the third trial, IPC devices were found to be superior to standard care in reducing the incidence of DVT, although they were associated with similar skin issues to GCS (Dennis et al., 2013). Similarly, the VICTORIAH trial found that a combination of IPC and GCS was more effective in reducing incident DVT than GCS alone (Lacut et al., 2005). While an older trial reported no significant difference between IPC and standard care in reducing DVT incidence (Prasad et al., 1982), it should be noted that it had considerably a smaller sample and poorer methodological quality than CLOTS3 and VICTORIAH.

Conclusions Regarding the Prevention of Venous Thromboembolism with Mechanical Devices

LoE	PICO statement	Number of RCTs	References
1a	There is conflicting evidence about the effect of **thigh-high graded compression stockings** to reduce the incidence of deep vein thrombosis when compared to **below-knee stockings.**	2	Azami et al. 2017; Dennis et al. 2010
1b	There is conflicting evidence about the effect of **intermittent pneumatic compression** to reduce the incidence of deep vein thrombosis when compared to **standard care.**	2	Dennis et al. 2013; Prasad et al. 1982
1a	**Graded compression stockings** may not reduce the incidence of deep vein thrombosis when compared to **standard care**.	2	Dennis et al. 2009; Muir et al. 2000

- The literature is mixed regarding the efficacy of intermittent pneumatic compression and graded compression stockings as an effective prophylactic intervention for deep vein thrombosis.

17.4.5 Treatment of Venous Thromboembolism Post Stroke

Heparinoids for Venous Thromboembolism Treatment
In a Cochrane review, Robertson and Jones (2017) compared the effects of fixed-dose subcutaneous LMWH and adjusted-dose intravenous/subcutaneous UFH for initial treatment of acute DVT or PE among patients with a range of diseases, not limited to stroke. A total of 29 RCTs (n=10390) of moderate quality were included in the review. In the initial treatment period and after 3-month follow-up, the rate of recurrent VTE was significantly lower in participants treated with LMWH than UFH. LMWH was also associated with a greater reduction in thrombus size and a lower rate of major bleeding when compared to UFH. However, the two treatments were similar in terms of mortality rates.

Oral Anticoagulation for Venous Thromboembolism Treatment
Dabigatran, an oral direct thrombin inhibitor, was studied in a non-inferiority trial compared to warfarin for the treatment of acute VTE (Schulman et al., 2009). In the RECOVER trial, patients in both groups were initially treated with parenteral anticoagulation for an average of 10 days, followed by either dabigatran (150mg twice daily) or warfarin (dosed to the International Normalized Ratio between 2-3). There was no significant difference between groups with respect to recurrent DVT, and both had similar safety profile with respect to episodes of any bleeding. As a result, the study concluded that fixed dose dabigatran is as effective as warfarin for the treatment of acute VTE (Schulman et al., 2009).

Rivaroxaban, an oral factor Xa inhibitor, has also been studied for the treatment of DVT and PE in the EINSTEIN trials. These open-label, non-inferiority trials compared rivaroxaban (15mg twice daily for 3 weeks, then 20mg once daily for a total of 6 months) to a standard therapy of subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for the same time frame. There was no difference in rate of recurrent DVT and risk of major bleeding between the groups (EINSTEIN Investigators, 2010). As well, the two groups had similar rates of recurrent PE, although the rivaroxaban group had fewer episodes of major bleeding than the standard therapy (EINSTEIN Investigators, 2010, 2013).

These agents would offer patients a safe and simple treatment alternative to vitamin K antagonist like warfarin, with no need for regular laboratory monitoring and a similar risk of bleeding. However, the use of these agents for this indication will depend on the country in which the physician is practicing, as this indication may not be accepted with the respective regulatory agencies.

Conclusions Regarding the Treatment of Venous Thromboembolism Post Stroke

- Venous thromboembolism may be treated with heparinoids or novel oral anticoagulants (e.g. dabigatran, rivaroxaban), although the research evidence is not specific to stroke.

17.5 Seizures Post Stroke

Seizures are episodes of abnormal electrical activity in the brain, which have been described as "*the clinical expression of excessive, hypersynchronous discharge of neurons in the cerebral cortex.*" (Wiebe & Butler, 1998). Given that strokes alter the brain parenchyma, they are a known structural risk factor for the development of seizures (Cordonnier et al., 2005). There is considerable variability in the reported incidence and timing of post-stroke seizures (PSS), and the impact of PSS on subsequent outcomes is unclear. While some studies reported that seizures were an independent risk factor for mortality (Bladin et al., 2000; Hamidou et al., 2013; Vernino et al., 2003), other studies failed to replicate these findings (Labovitz et al., 2001; Reith et al., 1997). As well, the risk of mortality associated with PSS may no longer be significant once adjusting for stroke severity and comorbidity (Hamidou et al., 2013).

17.5.1 Prevalence, Timing, and Risk of Seizures Post Stroke

In a case series, Wiebe and Butler (1998) observed that the incidence of seizures after ischemic or hemorrhagic stroke was highly variable, ranging from a low of 7.7% to a high of 42.8%. This variability is likely influenced by factors such as study design, patient population, diagnostic methods, and follow-up intervals. Compared to earlier studies, differences in stroke severity and increased survival may explain some of these differences (Lossius et al., 2002). Black et al. (1983) reported that 10% of all patients developed seizures post stroke: 39% occurred within the first 24 hours of stroke onset, 57% within the first week, and 88% within the first year. In a study of patients after intracranial hemorrhage, Sung and Chu (1989) found that seizure onset time was very similar: 30% in the first 24 hours, 60% in the first two weeks, and 90% in the first year. Following subarachnoid hemorrhage, Sundaram and Chow (1986) found that 84% of PSS took place within the first 2 weeks of stroke.

In comparison to earlier studies, recent reports reveal less variability in the risk of post-stroke seizures (PSS). The average risk of PSS is 10% within 9-10 years post stroke, and well-conducted prospective studies report a 5-year cumulative incidence of 11.5% (Burn et al., 1997). At least two studies suggested a higher incidence of PSS (15-17%) in patients in rehabilitation units (Kotila & Waltimo, 1992; Paolucci et al., 1997). It is not clear whether this finding reflects ascertainment bias, in which seizures are less likely to be missed in these closely observed patients, or a true increased seizure risk in this population, possibly related to greater stroke severity in inpatient rehabilitation. Table 17.5.1.1 lists the reported rates of PSS from several studies.

Table 17.5.1.1 Rate of Seizures/Epilepsy Post Stroke

Author, Year Sample Size	Rate of Seizures (or Epilepsy)	Duration/Timing of Follow-Up
Holmes et al. (1980) N=250	• 21%	• 2 years

de Reuck et al. (1980) N=240	• 7.9%	• Until death
Black et al. (1983) N=827	• 10% • Of these, 57% early onset	• 2 to 5 years
Olsen et al. (1987) N=77	• 9%, epilepsy	• 2 to 4 years
Gupta et al. (1988) N=90	• 100%, initial • 39%, recurrent • 33%, early onset • 67%, late onset	• 1 month to 13 years
Viitanen et al. (1988) N=409	• 3±2%, epilepsy at 1 year • 5±4%, epilepsy at 5 years	• 1 to 5 years
Kotila & Waltimo (1992) N=200	• 17%	• Unspecified follow-up
Lancman et al. (1993) N=219	• 10% • Of these, 54.55% early onset	• 1 month to 6 years
So et al. (1996) N=235	• 5%, recurrent • 6%, early onset • 3%, late onset	• Until death
Burn et al. (1997) N=675	• 2%, initial • Of these, 5% recurrent	• 2 years
Paolucci et al. (1997) N=306	• 15%	• 1 year
Teasell et al. (1999) N=536	• 7.8%	• 1 year
Bladin et al. (2000) N=1897	• 8.9%	• 9 months
Lossius et al. (2002) N=550	• 3.3%	• 1 year
Vespa et al. (2003) N=109	• 27.8% of hemorrhagic stroke • 6% of ischemic stroke	• No follow-up
Cordonnier et al. (2005) N=202	• 5.4%, early onset • 6.9%, late onset	• 3 years
Alberti et al. (2008) N=638	• 4.8%, early onset	• No follow-up
Szaflarski et al. (2008) N=6044	• 3.1%	• No follow-up
Burneo et al. (2010) N=5027	• 2.7%	• No follow-up
Krakow et al. (2010) N=58874	• 5.1% of hemorrhagic stroke • 2.2% of ischemic stroke	• No follow-up
Beghi et al. (2011) N=714	• 6.3%	• Unspecified follow-up
Chen et al. (2012) N=4126	• 2.6%	• 5 years
Procaccianti et al. (2012) N=66	• 3.2%	• 4 years
Alvarez et al. (2013b) N=128	• 1.2%	• 7 days
Arntz et al. (2013) N=697	• 11.3%	• 9 years
Jungehulsing et al. (2013) N=1020	• 8.2%, epilepsy	• 2 years

Haapaniemi et al. (2014) N=1317	• 11% <7 days • 9.2% >7 days • 7.1% at 1 year • 10.0% at 2 years • 10.2% at 3 years • 11.0% at 4 years • 11.8% at 5 years	• 5 years

Timing of Seizures Post Stroke

The majority of seizures are an isolated event post stroke, and may be partial or generalized (Ferro & Pinto, 2004). Most seizures occur within the first year of stroke onset, although the exact timing varies considerably (Procaccianti et al., 2012). Some of the variability in timing is due to lack of consistent definitions of early and late seizures. Across studies, early seizures have been defined as those occurring within 24 hours to as late as one month post stroke, while late seizures are most commonly identified as those occurring after two weeks. Table 17.5.1.2 presents the incidence of seizures grouped according to time post stroke.

Table 17.5.1.2 Timing of Seizures Post Stroke - Camilo & Goldstein (2004)

Time	Incidence of Seizure
< 24 hours	4.9% (So et al. 1996) 2% (Burn et al. 1997); increased to 3% after 24 hours 3.1% (Szaflarski et al. 2008) 6.3% (Beghi et al.2011)
< 48 hours	2.2% (Arboix et al. 2003)
<72 hours	19.2% (Vespa et al. 2003)
< 1 week	6% (So et al. 1996); decreased to 5% after 1 week 3.1% (Labovitz et al. 2001) 2.4% (Lamay et al.2003); increased to 3.4% after 1 week 5.4% (Cordonnier et al. 2005) 4.8% (Alberti et al. 2008) 3.2% (Procaccianti et al. 2012) 3.9% (Pezzini et al. 2013) 1.2% (Alvarez et al. 2013) 11% (Haapaniemi et al. 2014)
< 2weeks	6.5% (Kilpatrick et al. 1990) 2.5% (Kotila & Waltimo 1992) 4.2% (Reith et al. 1997) 33% (Gupta et al. 1998); increased to 67% after 2 weeks 4.8% (Bladin et al. 2000); decreased to 3.8% after 2 weeks 6.9% (Cordonnier et al. 2005) 4.8% (Alberti et al. 2008) 2.2% for ischemic stroke; 5.1% for hemorrhagic (Krakow et al. 2010) 3.1% (Hamidou et al. 2013) 9.2% (Haapaniemi et al. 2014)
1 month	5.5% (Lancman et al. 1993)
1 year	3% (Viitanen et al. 1988) 15% (Paolucci et al. 1997) 7.8% (Teasell et al. 1999) 3.3% (Lossius et al. 2002)
5 years	5% (Viitanen et al. 1988) 2.6% (Chen et al. 2012)

Risk Factors for Seizures Post Stroke

Several studies have examined risk factors for stroke to aid in identifying patients who are at increased risk of developing seizures post stroke. Despite considerable variability in the definitions and methodology between studies, common risk factors have emerged from the literature: cortical strokes, severe strokes, greater disability, and younger age. Stroke type may also predict seizure development, with hemorrhagic strokes being more likely than ischemic strokes (Alvarez et al., 2013a).

In a prospective study of 1640 patients presenting with first stroke, Giroud et al. (1994) found that younger patients and male patients were at increased risk of PSS. Arboix et al. (1997) had similar findings in a prospective study of 1220 patients with first stroke, identifying younger and male patients as at higher risk of seizure. This study also found that larger strokes, cortical strokes, and acute confusion were associated with PSSS, but that only the latter two factors on neuroimaging were predictive of seizure development (Arboix et al., 1997). As well, Lamy et al. (2003) identified cortical strokes, large strokes, and early-onset seizures as independent risk factors for later seizures, with a 4.5- to 10-fold increase in risk (Lamy et al., 2003).

The Copenhagen Stroke Study, a community-based, prospective study of 1197 patients with acute stroke, identified stroke severity as the single largest risk factor for early PSS (Reith et al., 1997). In two large population-based studies, younger age and stroke severity were found to be predictors of seizures post stroke occurring within 24 hours (Krakow et al., 2010; Szaflarski et al., 2008). One of these studies also found acute, non-neurologic infection and history of previous TIA to be predictive of developing PSS in both hemorrhagic and ischemic stroke (Krakow et al., 2010).

In a cohort of patients from the Registry of the Canadian Stroke Network (Burneo et al., 2010), stroke severity, hemorrhagic stroke, and neglect were found to be independent predictors of PSS during the initial period of hospitalization post stroke. A population-based, case-control study of 2327 patients with ischemic stroke found that the overall incidence of seizure was 1.2% (Alvarez et al., 2013a). The odds of PSS among patients who had received thrombolytic therapy were significantly higher, with an odds ratio of 4.6 in multivariate analysis. Similar to previous findings, Alvarez et al. (2013a) found that cortical stroke was also predictive of PSS.

Conclusions Regarding the Prevalence, Timing, and Risk of Seizures Post Stroke

- Post-stroke seizures occur is a less common complication post stroke, although the rates vary widely across studies and stroke onset.
- Common risk factors for post-stoke seizures include cortical strokes, severe strokes, greater disability, and younger age.

17.5.2 Pathophysiology of Seizures Post Stroke

Seizures in Hemorrhagic Stroke

Stroke type likely plays a role in the risk of developing PSS. The incidence of seizure following hemorrhagic stroke is estimated to be between 4% and 27.8% (DeHerdt et al., 2011; Vespa et al., 2003). The results from some studies support that hemorrhagic stroke increases the risk of early seizure (Beghi et al., 2011; Burneo et al., 2010; Kilpatrick et al., 1990; Vespa et al., 2003). However, other studies have not found hemorrhage stroke to be a significant risk factor for seizures post stroke (Alberti et al., 2008; Black et al., 1983; Olsen et al., 1987; Shinton et al., 1988). Some authors propose that hemorrhagic strokes are often more severe, and thus stroke severity accounts for the increase risk; others have proposed that hemorrhagic strokes cause more direct toxicity and irritation to surrounding brain parenchyma, thereby increasing the risk.

In patients with intracerebral hemorrhages, Reith et al. (1997) found a higher frequency of early seizures (within 14 days of onset) when compared to those with cerebral infarction. However, in multivariate analysis, initial stroke severity was the sole predictor of early PSS; the apparent increased frequency of PSS with hemorrhage reflected a higher initial stroke severity in this group of patients. A later study by Bladin et al. (2000) noted that patients who had suffered from a hemorrhagic stroke had an almost two-fold risk of developing a seizure compared to ischemic stroke. In this study, seizures after hemorrhagic stroke were more common in cortical lesions, but not specifically related to stroke severity.

A prospective study of 58874 patients with acute stroke in Germany demonstrated a two-fold increase in the incidence of seizure in hemorrhagic compared to ischemic strokes (Krakow et al., 2010). A retrospective, population-based study 6044 patients with no prior seizure history in USA also identified a statistically significant increase in seizure risk for patients with hemorrhagic strokes compared to all other stroke subtypes (Szaflarski et al., 2008). As well, in a cohort of 4126 patients, Chen et al. (2012) noted that the adjusted hazard ratio for developing PSS within five year follow-up was highest for patients with intracerebral hemorrhage.

Seizures in Cortical Stroke

The results of some studies have shown that PSS only occurred in patients with cortical involvement (Kilpatrick et al., 1990; Lancman et al., 1993). Olsen et al. (1987) found that a lesion involving the cerebral cortex, irrespective of size, was a prerequisite for the development of epilepsy. This concept was supported by Kilpatrick et al. (1990), who reported an absence of seizure activity among 1,000 patients with subcortical vascular strokes. For patients with hemorrhagic strokes, cortical involvement appeared to be associated with the development of seizures, since deep-seated hemorrhages rarely cause seizures (Kilpatrick et al., 1990; Olsen et al., 1987; Sung & Chu, 1989).

Many studies have demonstrated that cortical lesions are an independent risk factor for seizure post stroke (Alvarez et al., 2013a; Arboix et al., 1997; Bladin et al., 2000; Burneo et al., 2010; Lamy et al., 2003). Conceptually, cortical strokes as a risk factor for seizures is plausible: cortical insults increase the risk of abnormal electrical activity, and seizures are the result of abnormal electrical activity in the cerebral cortex. However, not all studies have demonstrated this relationship (Gupta et al., 1988; Shinton et al., 1988). Alberti et al. (2008) reported that early seizures occurred more frequently in patients with cortical involvement in univariate analysis, but the association disappeared when controlling for other variables. The exact nature of this relationship is not entirely clear, but research favours the finding that cortical stroke is a risk factor for seizure.

Seizure Type Post Stroke

A meta-analysis by Wiebe-Velazquez and Blume (1993) totalled the frequency of various seizure types post stroke from seven studies. From the combined 231 patients, 50% had simple partial seizures, 32% had primary generalized seizures, 15% had partial seizures with secondary generalization, and 2.5% had complex partial seizures. In a prospective study of 1640 patients with first stroke, Giroud et al. (1994) found that 61% of patients had simple partial seizures, 28% had partial seizures with secondary generalization, and 11% had generalized tonic-clonic seizures. In the Copenhagen Stroke Study, 40% of patients had only a single seizure; 68% of seizures were simple partial seizures with or without secondary generalization and 22% of seizures were primary generalized tonic-clonic seizures (Reith et al., 1997). Anticonvulsant therapy was initiated within two weeks of stroke onset in 86% of the patients who developed seizures in the post-stroke period (Reith et al., 1997).

Conclusions Regarding the Pathophysiology of Seizures Post Stroke

- The majority of seizures post stroke are simple partial seizures.
- Post-stroke seizures appear to be more common in hemorrhagic and cortical strokes, although this may be more directly related to stroke severity rather than etiology or location.

17.5.3 Prevention and Treatment of Seizures Post Stroke

Few studies have examined the treatment of PSS. Evidence to support definitive recommendations is lacking; thus clinical guidelines for seizure management are often based on clinical judgment and established management in other types of seizure disorders (Gilad, 2012). Acutely, standard therapy for aborting seizures begins with a benzodiazepine (e.g. lorazepam, diazepam) delivered via intravenous, sublingual, buccal, or rectal route. Lorazepam may be more effective in terminating status epilepticus (59-89%) compared to diazepam (43-76%) (Bluvol & K., 2003). Additional management varies with the severity of the clinical situation and the institution in which the stroke occurs.

Antiepileptic or anticonvulsant medications are considered for seizure prophylaxis in patients with multiple or recurrent seizures, or who are at increased risk of seizure. Studies have documented the rates of antiepileptic medication initiation for PSS, with significant variability. For instance, Reith et al. (1997) reported that 86% of patients with PSS were started on an antiepileptic medication. This reflects the common practice of treating patients empirically if their seizure is in the setting of stroke, as it is a known risk factor for recurrent seizures. However, there is some concern that the use of antiepileptic agents may impair post-stroke recovery (Camilo & Goldstein, 2004), which is an important consideration given that few post-stroke seizures are likely to recur (Silverman et al., 2002).

RCTs of antiepileptic medications post stroke have yet to identify optimal therapy. However, Gupta et al. (1988) found that 88% of patients with PSS were adequately managed with monotherapy. The selection of a patient's antiepileptic should be tailored to their existing medications and medical comorbidities (Silverman et al., 2002). For instance, phenytoin interacts with warfarin, which many patients may use for anticoagulation post stroke. It has also been noted that enzodiazepines should not be used as long-term antiepileptic therapy in PSS (Gilad, 2012; Silverman et al., 2002).

In a Cochrane review, Sykes et al. (2014) sought to examine the efficacy of antiepileptic drugs for prevention or treatment of PSS. Only one study was found to be suitable for review: a prospective, randomized, double-blind, placebo-controlled trial for primary prevention of seizures post stroke; the study compared valproic acid to placebo in 72 patients with intracerebral hemorrhage (Gilad et al., 2011). The authors concluded that there is insufficient evidence to support the routine use of antiepileptic therapy for primary or secondary prevention in patients with PSS. The evidence was also insufficient to aid in the selection of antiepileptic drugs for the management of PSS.

Table 17.5.3.1 Summary of RCTs Evaluating Prevention and Treatment of Seizures Post Stroke

Authors (Year) Study Design (PEDro Score) Sample Size_start Sample Size_end Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)

Gilad et al. (2011) RCT (6) N=84	E: Valproic acid C: Placebo	• NIH Stroke Scale (+exp) • Seizures (-)
Gilad et al. (2007) RCT (3) $N_{start}=64$ $N_{end}=64$ TPS=Chronic	E1: Lamotrigine E2: Carbamazepine Duration: 100mg/d of Lamotrigine, 7d/wk for 12wk OR 300mg/d of Carbamazepine for 12wk Statistical Analysis: Independent T-Test	• Reduction of Adverse Events: $(+exp_1)$ • Seizure-free patients (-)
Rowan et al. (2005) RCT (9) $N_{start}=593$ $N_{end}=NR$ TPS=Chronic	E1: Lamotrigine E2: Gabapentin E3: Carbamazepine Duration: 150mg/d (Lamotrigine), 7d/wk for 52wk OR 1500mg/d (Gabapentin), 7d/wk for 52wk OR 600mg/d (Carbamazepine), 7d/wk for 52wk Statistical Analysis: Fisher's Exact Test	• Reduction of Adverse Events: $(+exp_1, +exp_2)$ • Seizures (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
$+exp_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

The Early Treatment with Levetiracetam After Stroke (ETLAS) trial by van Tuijl et al. (2011) was initiated aiming to determine whether treatment with levatiracetam was superior to placebo for primary prevention of PSS. However, the trial did not meet the intended sample size due to various factors, and the authors concluded that a prophylactic trial was not feasible in patients post stroke (van Tuijl et al., 2011). Three other RCTs have evaluated the efficacy of anticonvulsant therapy in the post-stroke population (Gilad et al., 2011; Gilad et al., 2007; Rowan et al., 2005).

In elderly patients with seizures, Rowan et al. (2005) compared the effectiveness of gabapentin, lamotrigine, and carbamazepine as treatment; cortical stroke was the etiology for seizures in most patients. Although seizure control was similar between the groups, compliance was best in the lamotrigine group and tolerance was worst in the carbamazepine group (Rowan et al., 2005). Gilad et al. (2007) compared monotherapy with lamotrigine to carbamazepine in patients with PSS. There was a non-significant improvement in seizure control in the lamotrigine group relative to carbamazepine: 72% versus 44% seizure free, respectively (Gilad et al., 2007). Similar to Rowan et al. (2005), the authors reported that lamotrigine was better tolerated (Gilad et al., 2007). A subsequent RCT by Gilad et al. (2011) compared valproic acid to placebo for primary prevention of PSS in patients with hemorrhagic stroke. In total, 21% of patients developed seizures; the study did not detect a difference between valproic acid and placebo.

Conclusions Regarding the Prevention and Treatment of Seizures Post Stroke

There is Level 1b and Level 2 evidence that lamotrigine, gabapentin, and carbamazepine are similar in reducing the rate of recurrent post-stroke seizures, but carbamazepine is more poorly tolerated.

There is Level 1b evidence that valproic acid does not prevent post-stroke seizures when compared to placebo, but may confer neuroprotective effects.

LoE	PICO statement	Number of RCTs	References
1b	**Lamotrigine, gabapentin, and carbamazepine** have similar rates of efficacy in reducing the rate of recurrent post-stroke seizures, but **carbamazepine** is more poorly tolerated.	2	Gilad et al. 2007; Rowan et al. 2005
1b	**Valproic acid** may not have a difference in preventing recurrent post-stroke seizures when compared to a **placebo.**	1	Gilad et al. 2011

- Insufficient evidence exists to guide selection of monotherapy for antiepileptic medications in patients with post-stroke seizures.
- Treating all stroke patients with anticonvulsants as primary seizure prophylaxis is not recommended.
- Decisions to initiate antiepileptic therapy should be tailored to patients' individual needs.

17.6 Osteoporosis Post Stroke

Osteoporosis is a disease of decreased bone mass, quantified as diminished bone mineral density (BMD). It is associated with significant complications, including hip fractures and mortality (Carda et al., 2009). Osteoporosis is a well-recognized complication post stroke, and has a distinct pathophysiology and clinical presentation that predisposes them to a higher risk than in the non-stroke population (Carda et al., 2009). In a group of patients admitted for inpatient stroke rehabilitation, Watanabe (2004) found that 40% already had osteoporosis. These findings highlight the importance for screening for bone loss in patients post stroke. Unfortunately, few stroke management guidelines include recommendations regarding post-stroke osteoporosis (Borschmann et al., 2012).

17.6.1 Pathophysiology of Osteoporosis Post Stroke

During the first year post stroke, subjects can lose from 3.6% to 17% of their BMD (Carda et al., 2009). Considerable evidence suggests that loss of BMD preferentially occurs in paretic limbs (Beaupre & Lew, 2006; De Brito et al., 2013; Demirbag et al., 2005; Hamdy et al., 1993; Jorgensen et al., 2000; Liu et al., 1999; Pang et al., 2013; Ramnemark et al., 1999; Sato et al., 1996; Yavuzer et al., 2002), even when controlling for disuse (Pang et al., 2013). For instance, Hamdy et al. (1993) reported a significant difference in BMD for both the affected upper limb (7.95%) and lower limb (3.42%) when compared to the non-affected limbs. As well, Beaupre and Lew (2006) found that the loss of BMD in the affected arm within the first year post stroke for some patients was equal to more than 20 years of bone loss for similar aged healthy individuals. These finding underscore the difference in clinical presentation of osteoporosis post stroke: upper limbs are disproportionately affected compared to the usual osteoporosis pattern for individuals without stroke (Carda et al., 2009). Even in patients without lower limb paresis, the ability to ambulate independently and low BMD are closely linked (Schnitzer et al., 2012).

Several studies have examined determinants of bone loss post stroke: advanced age; severity of hemiplegia; longer duration of immobility; lower vitamin D serum levels; and time since menopause in women (Carda et al., 2009; Levendoglu et al., 2004; Poole et al., 2002; Sato et al., 1999). Of these, reduced mobility and length of immobilization are purported to be the most significant risk factors (Carda et al., 2009; Del Puente et al., 1996). Immobility is thought to trigger

an increase in bone resorption, mediated by increased hyperparathyroidism (Massagli & Cardenas, 1999). This theory is supported by findings that the serum concentrations of bone resorption markers, such as intact parathyroid hormone and ionized calcium, were significantly higher in patients with stroke than in control subjects (Sato et al. 1998). Vitamin D deficiency, due inadequate dietary intake and sunlight deprivation, is also thought to contribute to post-stroke osteoporosis (Sato et al., 1996). Sato et al. (1996) found that patients with a history of stroke had significantly lower serum vitamin D levels than those without prior stroke (Sato et al., 1996). However, a retrospective, population-based study did not identify a relationship between osteoporosis and vitamin D deficiency; this may have been due to the very high rates of vitamin D deficiency (71%) (Uluduz et al., 2014).

Conclusions Regarding the Pathophysiology of Osteoporosis Post Stroke

- Osteoporosis is a common complication post stroke, particularly in the hemiparetic limbs.
- Compared to osteoporosis in the general population, post-stroke osteoporosis is associated with a considerably greater loss of bone mineral density.
- Risk factors for post-stroke osteoporosis include severity of hemiplegia, duration of immobility, and vitamin D deficiency.

17.6.2 Hip Fractures Post Stroke

Hip fractures are a common problem post stroke, related to high rates of osteoporosis, poorer mobility, and increased falls risks (Saverino et al., 2006). The risk of hip fracture post stroke has also been associated with advanced age, female gender, low pre-stroke functional status, poorer cognition, and diabetes mellitus (Dennis et al., 2002; Ishida et al., 1985; Kanis et al., 2001). Additional risk factors include perceptual deficits (Hemineglect), poor balance, depression, urinary incontinence, and various medications (Eng et al., 2008; Peszczynski, 1956; Peszczynski, 1957).

The incidence of hip fracture as a late complication of stroke is between 4% and 15%, with the majority of fractures occurring on the hemiparetic side (Chiu et al., 1992; Mulley & Espley, 1979; Peszczynski, 1957; Poplingher & Pillar, 1985). In a study of 1139 patients followed for a median of 3 years, Ramnemark et al. (1998) reported the risk of hip fracture to be 2-4 times higher among individuals post stroke compared to the general population. Similarly, Kanis et al. (2001) reported a 7-fold increase in hip fracture in the first year post stroke. Most post-stroke fractures are caused by accidental falls and tend to occur on the paretic side, likely related to more significant osteoporosis associated with paretic limbs, and possibly with poorer ability to break a fall using the ipsilateral hand (Poole et al., 2002).

Hip fractures are a major source of morbidity and mortality in patients post stroke (Beaupre & Lew, 2006). However, other osteoporotic fractures can also impair function and/or have significant clinical consequences. Radial fractures, which are more common in patients with upper extremity osteoporosis, may impair a person's ability to use their gait aid, leading to immobility and its associated adverse effects. Pang et al., (2013) found grip strength to be the strongest determinant of radius compressive bone strength index, offering an easy-to-administer assessment to screen patients who may have compromised upper extremity bone health post stroke.

Conclusions Regarding Hip Fractures Post Stroke

- Hip fractures are a common occurrence post stroke and associated with greater risk of morbidity/mortality.
- They are related to high rates of osteoporosis, increased risk of falls, and poorer mobility post stroke.

17.6.3 Treatment of Osteoporosis Post Stroke

Several therapeutic interventions intended to reduce the risk of osteoporosis and subsequent risk of hip fracture have been evaluated in RCTs: vitamin supplementation (B, D, and K), calcium supplementation, and bisphosphonates.

Table 17.6.3.1 Summary of RCTs Evaluating Treatments for Osteoporosis Post Stroke

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Vitamins		
Gommans et al. (2013) RCT (8) N$_{start}$=164 N$_{end}$=NR TPS=Acute	E: Vitamin B$_6$, B$_9$, or B$_{12}$ C: Placebo Duration: 25mg of B$_6$ (1x/d) for 104wk OR 2mg of B$_9$ (1x/d) for 104wk OR 500μg of B$_{12}$ (1x/d) for 104wk	• Osteoporotic Fracture Incidence (-)
Sato et al. (1998) RCT (5) N=108	E: Vitamin K$_2$ C: No treatment	• Bone Mineral Density (+exp) • Biochemical markers (+exp) • Hip fracture (-)
Sato et al. (1997) RCT (8) N=84	E: Vitamin D$_3$ + Calcium C: Placebo + Calcium	• Bone Mineral Density (+exp) • Hip fracture (+exp)
Biphosphates		
Sato et al. (2010) RCT (8) N=40	E: Etidronate C: Placebo	• Bone Mineral Density (+exp) • Hip fracture (-)
Poole et al. (2007) RCT (9) N$_{start}$=31 N$_{end}$=27 TPS=Acute	E: Zoledronate (infusion) C: Placebo Duration: 4mg/d of Zoledronate (intravenously), 1x (35d after stroke) OR 4mg of placebo (intravenously), 1x (35d after stroke)	• Bone Mineral Density (+exp) • Hip fracture (-)
Ikai et al. (2001) PCT N$_{start}$=81 N$_{end}$=72 TPS=Acute	E: Etidronate C: Placebo Duration: 200mg/d OR 400mg/d of etironate 7d/wk for 12wk OR 200mg/d OR 400mg/d of placebo 7d/wk for 12wk	• Bone Mineral Density (-)
Calcitonin		
Uebelhart et al. (1999) RCT (5) N$_{start}$=34 N$_{end}$=23 TPS=Acute	E: Salmon Calcitonin +Oral Calcium C: Placebo + Oral Calcium Duration: 200 IU/d of salmon calcitonin + 1000mg of oral calcium/d, 7d/wk for 104wk OR 200 IU/d of placebo + 1000mg of oral calcium/d, 7d/wk for 104wk	• Serum Total Alkaline Phosphatase (-) • Serum Osteocalcin (-) • Serum carboxy-terminal extension peptide of Type-I procollagen (-) • Serum cross-linked carboxy-terminal telopeptide of Type-I collagen (-) • Calcium/Creatinine Levels (-) • Hydroxyproline/Creatinine (-) • Serum amino-terminal extension peptide of Type-III procollagen (-)

Weight training		
[Han et al. (2017)](#) RCT (4) N_{start}=129 N_{end}=129 TPS=Acute	E: Male or female weight training for 30min E2: Male or female weight training for 60min E3: Male or female weight training for 90min Duration: 5d/wk for 3mo	E3 vs E2/E1: • Bone mineral density (+exp_3) • E2 vs E1: • Bone mineral density (+exp_2)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp_2 indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Discussion

Bisphosphonates prevent osteoporosis by inhibiting bone resorption by osteoclasts. Poole et al. (2007) noted that significant bone loss occurs early on post stroke when many patients have dysphagia. The authors hypothesized that an intravenous bisphosphonate would be an effective means to provide the treatment compared with tablet form in acute stroke. The treatment was effective in preventing BMD loss compared to placebo, although its effect on reducing hip fractures is unknown as they did not occur in either group (Poole et al., 2007). In a non-randomized controlled trial of inpatient stroke rehabilitation, Ikai et al. (2001) found that BMD was less likely to decline over three months in those who received two weeks of etidronate therapy compared to those who received placebo. In a more recent study, Sato et al. (2010) found that etidronate increased BMD on the hemiparetic side of patients with stroke by 1.4% over 2 years, compared with a decrease in BMD of 2.2% in those receiving placebo. The event rate for hip fractures was too low to identify a definitive benefit for the bisphosphonate over control.

Vitamin D supplementation is recommended for preventing osteoporosis in areas, such as Canada, where exposure to sunlight is insufficient to generate adequate vitamin D in the skin (Brown & Josse, 2002). Vitamin D increases calcium absorption from the gut and promotes bone mineralization while inhibiting bone resorption (Brown & Josse, 2002; Holick, 2007). Comparing combined calcium and vitamin D supplementation to calcium and placebo post stroke, Sato et al. (1997) reported that patients who received the combined treatment experienced significantly less loss of BMD on both the paretic and non-paretic sides than controls. As well, no patients treated with vitamin D fractured their hip during the study period compared to four patients in the control group (Sato et al., 1997). Calcitonin is a hormone that regulates serum levels of calcium and phosphate, and it has been shown to inhibit bone resorption (Chambers & Magnus, 1982). A single trial found that intranasal calcitonin did not improve favourable bone metabolism when compared to placebo (Uebelhart et al., 1999).

Vitamin K is essential for Gla protein carboxylation, which is required to develop bone matrix; reduced levels of circulating Gla protein have been associated with increased risk of hip fractures (Shearer, 1995). When compared to no treatment, vitamin K supplementation was associated with reduced BMD loss and altered levels of biochemical markers indicating bone metabolism (Sato et al., 1998). Vitamin B is believed to modulate the formation of collagen or alter osteoblast metabolism (Kim et al., 1996). However, its exact mechanism in bone metabolism is not well characterized and its level of impact on BMD is not fully established (Bailey & van Wijngaarden, 2015). In patients with acute or subacute stroke, B vitamins (B9, B6, or B12) were found to be no more effective than placebo in reducing the risk of bone fracture (Gommans et al., 2013).

In Canada, the Scientific Advisory Council of Osteoporosis Canada released updated guidelines for the diagnosis and management of osteoporosis (Papaioannou et al., 2010). The guidelines do not offer stroke-specific recommendations, but do recommend screening for osteoporosis in all

patients who have a disorder strongly associated with rapid bone loss, such as stroke. Pharmacological interventions including bisphosphonates and vitamin D are recommended as first line treatment for osteoporosis (Papaioannou et al., 2010). Given that the guidelines are not specific to stroke, clinicians should exercise caution with other recommended therapies, such as supplemental estrogens, as these are not generally recommended in the post-stroke population.

Conclusions Regarding the Treatment of Osteoporosis Post Stroke

LoE	PICO statement	Number of RCTs	References
1a	**Vitamin K$_2$, and vitamin D$_3$ with calcium** may improve bone mineral density when compared to **placebo or no treatment**.	2	Sato et al. 1998; Sato et al. 1997
1a	There is conflicting evidence about the effect of **biphosphates (Etidronate, Zoledronate)** on improving bone mineral density when compared to **placebo.**	3	Sato et al. 2010; Poole et al. 2007; Ikai et al. 2001
2	**Salmon calcitonin combined with oral calcium** may not have a difference when compared to **oral calcium** for improving bone tissue metabolism.	1	Uebelhart et al. 1999
2	**Weight training of higher intensities** may improve bone mineral density than **weight training of lower intensities**.	1	Han et al. 2017

- Vitamins K$_2$ and D$_3$, as well as high intensity weight training may improve bone mineral density.
- While the literature is mixed on the effect of biphosphates to improve bone mineral density.

17.7 Central Pain States Post Stroke

Over a century ago, two French neurologists described an intractable and distressing pain disorder after thalamic stroke in "Le syndrome thalamique" (Dejerine & Roussy, 1906). Since their initial description of pain after thalamic stroke, additional stroke-specific pain syndromes have been described including complex regional pain syndrome, hemiplegic shoulder pain, spasticity-related pain, myofascial pain syndrome, persistent headache, post-stroke back pain, and central post-stroke pain (CPSP).

CPSP is a specific type of neuropathic pain that is thought to be due to stroke-related injury to pathways or brain centres involved in pain processing (de Oliveira et al., 2012; Henry et al., 2008). In this condition, pain and sensory abnormalities occur in the parts of the body that correspond to the stroke lesion (Klit et al., 2009). In 40-60% of patients, the onset of pain occurs more than one month after the stroke (Hansson, 2004). Delayed onset combined with language or cognitive impairments, prioritization of other medical complications, and depression have been postulated to contribute to underdiagnosis and undertreatment of this debilitating pain (Hansson, 2004; Henry et al., 2008; Jensen & Lenz, 1995; Segatore, 1996).

17.7.1 Prevalence of Central Post-Stroke Pain
The prevalence of CPSP varies by study, occurring in 2-8% of patients with stroke (Henry et al., 2008; Mucke & Maciewicz, 1987; Pagni, 1976; Schott, 1996; Tasker, 1990). Some research has reported rates as high as 35% among stroke patients, with up to 5% reporting moderate to severe pain (Andersen et al., 1995; Widar & Ahlstrom, 2002). Although CPSP is generally considered rare, some authors argue that it is not getting the attention it deserves (Bowsher, 2001).

The largest prospective cohort study of chronic pain syndromes to date, the Prevention Regiment for Effectively avoiding Second Stroke (PRoFESS) trial, reported that the incidence of new chronic post-stroke pain from total of 15,754 participants was 10.6% (O'Donnell et al., 2013). The authors further identified the incidence of post-stroke pain subtypes: 2.7% for CPSP; 1.5% for peripheral neuropathic pain; 1.3% for spasticity-related pain; 0.9% for shoulder subluxation pain; and 4.7% for all other pain syndromes combined. Risk factors associated with any post-stroke pain condition included increased stroke severity, female sex, alcohol intake, previous depression, hyperlipidemia, diabetes mellitus, peripheral vascular disease, and prescription of aspirin/dipyridamole. The prevalence, incidence, and clinical features of CPSP are shown in Table 17.7.1.1.

Table 17.7.1.1 Summary of Prevalence, Incidence, and Clinical Presentation of CPSP

Author, Year Sample Size	Prevalence (P), Incidence (I), and/or Clinical Presentation of CPSP/Pain
Boivie et al. (1989) N=27	• 92% had raised thresholds to thermal pain • 96% had abnormal sensibility to pin prick stimulus • 50% had radiation of stimuli • 45% had after-sensations • 41% had paraesthesia • 23% had allodynia
Andersen et al. (1995) N=267	P_{CPSP}= 8% • Presence was not related to age, lesion size, or side of stroke • Onset was acute in 63%, subacute in 19%, and chronic in 19% • 42% had abnormal sensory signs at least once, who were more likely to have acute onset extremity paresis and greater levels of disability at 1mo
Vestergaard et al. (1995) N=11	• 90.9% had increased cold detection threshold • Warmth detection threshold was higher in the pain area in all patients • Median spontaneous pain intensity on a visual analogue scale was 3.3 (range: 0-7.7)
Bowsher et al. (2001) N=1071	P_{CPSP}=11% • 25% of CPSP had thermal pain • 25% of CPSP had plegia in painful limb • 75% of CPSP had paresis in painful limb
Widar et al. (2002) N=43	P_{CPSP}=2.8% of all patients P_{CPSP}=35% of patients with pain • 93% of CPSP had sensory abnormalities (allodynia, hypoalgesia, hyperalgiesa) • Thermal sensibility was significantly reduced on the symptomatic side in CPSP
Jonsson et al. (2006) N=297	P_{Pain} =32% at 4 months, 21% at 16 months • Predictors of pain were younger age, female sex, higher NIHSS, and higher HbA1c at onset • Predictors of severe pain were female sex, higher Geriatric Depression Scale score, higher Mini Mental State Exam score, and higher HbA1c at 16mo
Klit et al. (2011) N=964	P_{CPSP}=4.4% definite, 7.3% probable, 8.9% possible • 66% of CPSP had allodynia or hyperalgesia • 80% of CPSP had allodynia or evoked dysesthesia in at least one sensory modality • 40% of CPSP had allodynia to cold and 66% had dysesthesia to cold • 57% of CPSP had pinprick hyperalgesia
O'Donnell et al. (2013) N=15754	I_{Pain}= 10.6% I_{CPSP}=2.7% • For non-CPSP pain syndromes: 1.5% had peripheral neuropathy; 1.3% had spasticity-related pain, 0.9% had shoulder pain, and 4.7% had other pain syndromes
Raffaeli et al. (2013) N=601	P_{CPSP}=11%

	• Pain onset was immediately post stroke in 57.6%, 1mo post stroke in 19.7%, and several months post stroke in 19.7% • Continuous pain was present in 59.6% of CPSP patients and intermittent pain was present in 36.5%	
Harno et al. (2014) N=824	P_CPSP=5.9% • Strong or very strong pain and sensory symptoms included tingling pain (54%), electric shocks (29%), warm or cold allodynia (29%), and numbness (46%) • Hypoesthesia to warm was prevalent in 62%, to cold in 43%, to pinprick in 28%, and to touch in 23% • Hyperesthesia to pinprick was found in 36%, to cold in 13%, and to warm in 13% • CPSP was associated with moderate to severe stroke symptoms and lower quality of life • 29.9% had sensory abnormality without CPSP • 64.2% had neither sensory abnormality nor CPSP	
Paolucci et al. (2016) N=546	P_Pain=29.56% • 14.06% had acute stroke, 42.73% had subacute stroke, and 31.9% had chronic stroke	

As outlined above, there is considerable variability in the prevalence and incidence of CPSP in the literature. Many authors identified that underdiagnosis of CPSP is plausible, as patients may have other conditions that healthcare providers prioritize over pain or may not be able to describe their pain (Hansson, 2004; Henry et al., 2008; Jensen & Lenz, 1995; Segatore, 1996). This hypothesis is supported by a study that allowed patients to self-identify as having post-stroke pain and found the prevalence of CPSP to be higher than previously expected (Bowsher, 2001). Other studies supported that excluded patients with cognitive or language difficulties also supported the hypothesis (Andersen et al., 1995; Raffaeli et al., 2013). Several studies attempted to characterize which patients develop CPSP and found that female sex, younger age, and severe stroke were associated with increased risk (Harno et al., 2014; Jonsson et al., 2006). Despite the limitations in determining its prevalence, CPSP warrants management.

Conclusions Regarding the Prevalence of Central Post-Stroke Pain

> • Central post-stroke pain is a less common complication post stroke, although prioritization of other conditions may lead to its underdiagnosis.

17.7.2 Pathophysiology of Central Post-Stroke Pain

Given that it was initially described as a result of thalamic stroke, CPSP is often referred to as thalamic pain. However, further understanding and evaluation have demonstrated that CPSP can arise from lesions outside of the thalamus (Agnew et al., 1983; Bowsher, 1985; Fields & Adams, 1974; Garcin & Lapresle, 1969; Leijon & Boivie, 1989a; Loh et al., 1981). CPSP is invariably associated with a lesion involving the spino-thalamo-cortical pathway, which is responsible for pain and temperature processing at different levels within the central nervous system (CNS), resulting in a disturbance in temperature and pain sensation (Andersen et al., 1995). Leijon et al. (1989b) showed that central pain states occurred following brainstem, thalamic, and suprathalamic (cortical) strokes.

At present, the pathophysiology of CPSP states remains unknown. It is becoming increasingly clear that damage to the spino-thalamico-cortical pathway is associated with CPSP, although not all patients with damage to this pathway will experience CPSP (Andersen et al., 1995; Boivie et al., 1989; Dejerine & Roussy, 1906; Jensen & Lenz, 1995; Vestergaard et al., 1995). CPSP is always associated with impaired sensory perceptions to temperature and painful stimuli, which are somatosensory functions mediated by the spinothalamic tract (Boivie, 1992; Boivie et al., 1989; Vestergaard et al., 1995). However, touch, vibration sense, and two-point discrimination

are generally regarded to be mediated by lemniscal pathways in the CNS that may remain intact (Boivie et al., 1989; Vestergaard et al., 1995).

Many cases of CPSP are associated with hyperalgesia and/or allodynia, despite sensory deficits in the affected areas due to stroke. This paradoxical presence of a sensory deficit in combination with hyperalgesia in the part of the body affected by the stroke lesion suggests a central sensitization of third and fourth order neurons in the central nervous system as a result of loss of spino-thalamic or thalamo-cortical input (Vestergaard et al., 1995). The loss of normal cortical or thalamic inputs or modulation to spinal sensory inputs may exaggerate the perception of pain; for instance, lack of cortical modulation due to stroke may lead to hyperexcitability of intact thalamic neurons, evoking a perception of pain to a harmless stimulus. This hypothesis shares many features thought to be characteristic of other neuropathic pain syndromes associated with peripheral nerve lesions where spinal cord neurons that have lost their afferent input develop hyperexcitability, producing pain (Bennett & Laird, 1992; Dubner, 1991; Wall, 1991).

Conclusions Regarding the Pathophysiology of Central Post-Stroke Pain

- The precise pathophysiology of central post-stroke pain is unknown, but it appears to be associated with a lesion involving the spino-thalamo-cortical pathway.

17.7.3 Clinical Features of Central Post-Stroke Pain

Neuropathic pain has different qualities than nociceptive pain: it may be described as a burning sensation, unpleasant tingling, pins and needles, or numbness. Terms such as ripping, tearing, pressing, twisting, aching, pricking, and lacerating have also been used to describe neuropathic pain (Andersen et al., 1995; Boivie et al., 1989; Leijon et al., 1989; Tasker, 1990). Dysesthesia are defined as unpleasant sensations, either spontaneous or evoked (Andersen et al., 1995). Allodynia refers to a painful or unpleasant somatosensory experience, often poorly localized, elucidated by normally non-painful stimuli (Andersen et al., 1995). Hyperalgesia is defined as an increased pain response to a painful stimulus (Andersen et al., 1995).

CPSP is experienced within an area smaller than the total area of sensory impairment; the pain may be constant or occur in spontaneous paroxysms of pain (Boivie et al., 1989; Frese et al., 2006; Leijon et al., 1989; Tasker, 1990). CPSP also can be exacerbated by physical movement, emotional stress, loud noises, light touch, extreme temperatures, and changes in the weather (Boivie et al., 1989; Leijon et al., 1989; Tasker, 1990). In a study of 23 patients with CPSP secondary to a known cerebrovascular lesion, Leijon et al. (1989) did not find that stroke location reliably predicted the description of pain, with the exception that "burning" pain was more commonly described with brainstem/suprathalamic lesions while "lacerating" pain was seen more with the thalamic lesions. Another study of 16 patients with CPSP noted no relationship between size or location of the stroke and the presence of CPSP (Andersen et al., 1995).

All patients with CPSP have some type of sensory abnormality on the affected side, almost always involving decreased perception of pain and temperature (Boivie et al., 1989). In addition to abnormalities of decreased sensory perception, nearly all patients with CPSP report spontaneous or evoked paresthesia and/or dysesthesia (Andersen et al., 1995; Leijon et al., 1989). Spontaneous dysesthesias occur in the majority of CPSP patients while almost all demonstrate some hypersensitivity to external somatic stimuli (Leijon et al. 1989). In fact, Anderson et al. (1995) noted that 56% of patients with CPSP reported allodynia to cold stimulation and 56% reported allodynia to touch.

While stroke-related sensory impairment is almost certain in CPSP, paralysis is variably present. The original thalamic pain syndrome described by Dejerine and Roussy (1906) was associated

with thalamic stroke and was characterized by mild hemiplegia, abnormal sensation, hemiastereognosia, intolerable pain, and hemiataxia with choreoathetoid movements (Andersen et al., 1995). One study of patients with CPSP found that 52% had no paresis, 37% had moderate paresis, and 11% had severe paresis (Leijon & Boivie, 1989a).

Central sensitization leading to pain post stroke has been thought to occur during neuronal recovery (Segatore, 1996). Few studies have closely examined the time required for the development of CPSP, but research supports the idea that CPSP develops early post stroke in the majority of patients, when neuronal recovery is most pronounced. Andersen et al. (1995) noted 63% of CPSP patients reported pain onset within one month of stroke, 19% between one and six months, and 19% after six months. A later, larger study of CPSP patients by Raffaeli et al. (2013) found that pain onset occurred immediately post stroke in 57.6% of patients, one month post stroke in 19.7%, and several months post stroke in 19.7%. In the Helsinki Young Stroke Registry, 5.9% of patients had CPSP; the majority developed pain within one month post stroke (Harno et al., 2014). Cumulatively, these studies favour early development of CPSP, but do not exclude the possibility of delayed symptom onset.

Conclusions Regarding Clinical Features of Central Post-Stroke Pain

- Central-post stroke pain generally involves some form of spontaneous and evoked sensory abnormality on the affected side including dysesthesia, allodynia, and hyperalgesia.
- Development of central post-stroke pain is most often within the first month of stroke onset.

17.7.4 Treatment of Central Post-Stroke Pain

Widar & Ahlstrom (2002) stated that "[p]ain after stroke is a symptom often forgotten…although it is reported to be a great problem in care." In the preceding sections, concerns regarding underdiagnosis of CPSP have been frequently noted. Indeed, diagnosis and identification of a clinical problem is crucial to its management. In addition to difficulty in ensuring that healthcare providers identify CPSP as a clinical problem for patients, inadequately effective treatments pose a considerable challenge to the management of CPSP. Due to its complex pathophysiology, which is not fully understood, a number of potential therapies have been investigated.

Surgical Intervention

A variety of operative treatments have been tried for CPSP including neurosurgical brain lesioning (Davis & Stokes, 1966; Mark et al., 1961; Nashold et al., 1969; White & Sweet, 1969) and stereotaxic chemical hypophysectomy (Levin et al., 1983). In uncontrolled studies, neurosurgical ablative procedures have been reported to have a 25% effectiveness rate in permanently relieving CPSP but were associated with a significant risk of brain injury (Pagni, 1976). These findings led to interest in the safety and efficacyof cortical stimulation.

Motor Cortex Stimulation

Since Tsubokawa et al. (1991) discovered that stimulation of the motor cortex was associated with inhibition of pain, it has been used to treat chronic thalamic pain due to a variety of causes, including CPSP. Invasive MCS involves a control device to regulate the degree and length of stimulation is implanted in the ipsilateral subclavicular thoracic area (Meyerson, 1979; Sweet, 1982). Although the direct mechanism through which MCS affects neuropathic pain is not well understood, it is believed to be associated with increased blood flow in the thalamus, brainstem, and cerebral cortex. Predicting which patients are most likely to benefit from MCS treatment is difficult. Sensitivity to barbiturates and opioids has been suggested as possible predictors of a positive response, while severe motor weakness may be a contraindication. Response to non-

invasive MCS can also be used to identify those who may be responsive to treatment. The European Federation of Neurological Societies has stated that there is Level C evidence of the efficacy of MCS in the treatment of chronic pain, and that it is useful in 50-60% of patients with CPSP with small risk of medical complications (Cruccu et al., 2007).

Repetitive transcranial magnetic stimulation (rTMS) provides a safer and less costly alternative to invasive MCS. Although mainly utilized for diagnostic purposes (Rossini & Rossi, 1998), early investigations of rTMS demonstrated pain reduction in some patients with central pain (Migita et al., 1995; Pascual-Leone et al., 1994). In a systematic review, Lima and Fregni (2008) examined the efficacy of both invasive and non-invasive brain MCS for the treatment of chronic pain. The mean percentage of positive responders among the 22 invasive studies was 64%, which was higher than the 40% of responders in the 11 noninvasive studies, suggesting that epidural (invasive) MCS was more effective. At follow-up, the percentage of responders in the invasive MCS group had decreased to 54.6%.

Pharmacological Treatment

Neuropathic pain such as CPSP creates challenges for involvement in rehabilitation (Cioni & Meglio, 2007). CPSP is caused by lesions located within nociceptive neuronal circuits that pass through the spinothalamic pathways at a higher level within the CNS (Katayama et al., 1998). Patients with CPSP commonly do not respond to other medical treatments and are usually resistant to opioid and nonsteroidal anti-inflammatory drug treatments. Though functional magnetic resonance imaging has increased understanding and specific localization of neuropathic pain, pharmacological treatments have made little improvement in pain reduction (Lazorthes et al., 2007).

Within the available literature on the pharmacological treatment of CPSP, there is significant variability in recommendations. A Cochrane review concluded that lamotrigine was not an effective treatment for post-stroke pain, based on the results from only a single RCT (Wiffen & Rees, 2007). Conversely, Kumar et al. (2009) concluded that amitriptyline and lamotrigine should be considered first-line drugs for CPSP. In a systematic review, Frese et al. (2006) examined studies investigating pharmacologic treatment of CPSP; seven small RCTs, six uncontrolled trials, and one case series were included. The authors reported that amitriptyline, lamotrigine, and gabapentin were effective oral medications for treating CPSP. Although lidocaine, propofol, and ketamine were effective for short-term control of CPSP, the authors found these options unsuitable for long-term use due to possible side effects and toxicity (Frese et al., 2006).

Table 17.7.4.1 Summary of RCTs Evaluating Treatments of CPSP

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Pharmacological Treatment		
Pregabalin/Gabapentin		
Kim et al. (2011) RCT (9) N$_{start}$=220 N$_{end}$=NR TPS=Chronic	E: Pregabalin C: Placebo Duration: 150mg/d to 600mg/d pregabalin, 7d/wk for 13wk OR 150mg/d to 600mg/d placebo, 7d/wk for 13wk	• Daily Pain Rating Scale (-) • Clinician Global Impression of Change (CGIC) (+exp) • Medical Outcome Study-Sleep (MOS-Sleep) (+exp) • Hospital Anxiety and Depression Scale-Anxiety (HADS-A) (+exp)
Vranken et al. (2008) RCT (9) N$_{start}$=40 N$_{end}$=27 TPS=Chronic	E1: Pregabalin (150mg/d) E2: Pregabalin (300mg/d) E3: Pregabalin (600mg/d) C: Placebo Duration: Start with 150mg/d, then titrated to 300mg/d, then titrated to a maximum of 600mg/d of pregabalin, 7d/wk for 4wk OR Start with 150mg/d, then titrated to 300mg/d, then titrated to a maximum of 600mg/d of placebo, 7d/wk for 4wk	• Visual Analog Scale (+exp) • EQ-5D (+exp) • SF-36 (Bodily Pain) (+exp) • Pain Disability Index (-)
Serpell et al. (2002) RCT (8) N$_{start}$=307 N$_{end}$=234 TPS=Chronic	E: Gabapentin C: Placebo Duration: Start at 900mg/d of Gabapentin (1x/d) for 3d, then 1800mg/d of Gabapentin (1x/d) for 2wk, then 2400mg/d of Gabapentin (1x/d) for 6wk for a total of 7d/wk for 8wk OR Start at 900mg/d of placebo (1x/d) for 3d, then 1800mg/d of placebo (1x/d) for 2wk, then 2400mg/d of placebo (1x/d) for 6wk for a total of 7d/wk for 8wk	• Clinician and Patient Global Impression of Change (+exp) • Visual Analog Scale (+exp) • Short-Form McGill Pain Questionnaire (+exp) • SF-36 (+exp)
Anticonvulsants		
Jungehulsing et al. (2013) RCT (8) N$_{start}$=42 N$_{end}$=33 TPS=Subacute	E: Levetiracetam (3000mg) C: Placebo (3000mg) Duration: Start at 500mg (2x/d) and then increase to 3000mg/d (Levetiracetam; during week 2), 7d/wk for 8wk + 2wk washout period and then a further 8wk (with the same prescription pattern) OR Start at 500mg (2x/d) and then increase to 3000mg/d (placebo) 7d/wk for 8wk + 2wk washout period and then a further 8wk (with the same prescription pattern)	• Likert Scale (-) • McGill Pain Questionnaire (-) • Beck Depression Index (-) • Short Form-12 Health Survey (-)
Vestergaard et al. (2001) RCT (8) N$_{start}$=31 N$_{end}$=26 TPS=Chronic	E: Lamotrigine (25mg, 50mg, 100mg, 200mg) C: Placebo (25mg, 50mg, 100mg, 200mg) Duration: 25mg/d of Lamotrigine (for 2wk), then 50mg/d of Lamotrigine (for 2wk), then 100mg/d of Lamotrigine (for 2wk), then a	• Median Pain Score (+exp) • Global Pain Score (+exp) • Assessment of Evoked Pain (+exp) • Areas of Spontaneous Pain (-) • Allodynia/Dysesthesia (-)

	maximum of 200mg/d of Lamotrigine (for 2wk) 7d/wk for 8wk + 2wk washout period and then a further 8wk (with the same prescription pattern) OR 25mg/d of placebo (for 2wk), then 50mg/d of placebo (for 2wk), then 100mg/d of placebo (for 2wk), then a maximum of 200mg/d of placebo (for 2wk) 7d/wk for 8wk + 2wk washout period and then a further 8wk (with the same prescription pattern)	
Amtriptyline		
Lampl et al. (2002) RCT (7) N_{start}=39 N_{end}=37 TPS=Chronic	E: Amitriptyline (75mg) C: Placebo (75mg) Duration: 75mg/d (1x/d) of amitriptyline 7d/wk for 52wk OR 75mg/d (1x/d) of placebo 7d/wk for 52wk	• Visual Analog Scale (-) • Average Time to Pain (-) • Hypoesthesia/Allodynia (-)
Leijon & Boivie (1989a) RCT Crossover (6) N_{start}=15 N_{end}=15 TPS=Chronic	E1: Amitriptyline (75mg/d) E2: Carbamazepine (800mg/d) C: Placebo Duration: 75mg/d (maximum dose) of Amitriptyline, 7d/wk for 4wk OR 800mg/d (maximum dose) of Carbamazepine, 7d/wk for 4wk OR placebo (dosage not specified), 7d/wk for 4wk	E1 vs E2/C • Verbal Rating Scale (+exp1) • Comprehensive Psychopathological Rating Scale (-)
Other drugs		
Cho et al. (2013) RCT (6) N_{start}=20 N_{end}=16 TPS=Chronic	E: Apitoxin (diluted in 0.005% saline) C: Saline Duration: 0.05mL (injection) of apitoxin, 2x/wk for 3wk OR 0.05mL (injection) of placebo, 2x/wk for 3wk	• Visual Analog Scale (+exp)
Vranken et al. (2011) RCT (9) N_{start}=48 N_{end}=48 TPS=Acute	E: Duloxetine C: Placebo Duration: 120mg/d of duloxetine (1x/d), 7d/wk for 4wk OR 120mg/d of placebo (1x/d), 7d/wk for 4wk	• Visual Analog Scale (-) • Global Impression of Change • Pain Disability Index (-) • EuroQol-5D (-) • Health Survey Questionnaire (SF-36) (-) • Health Survey Questionnaire (SF-36 Bodily Pain) (+exp)
Vranken et al. (2005) RCT (9) N_{start}=33 N_{end}=33 TPS=Acute	E1: S (+)-Ketamine (50mg) E2: S (+)-Ketamine (75mg) C: Placebo Duration: 50mg of S (+)-ketamine 7d/wk for 4wk OR 75mg of ketamine S (+)-ketamine 7d/wk for 4wk OR placebo, 7d/wk for 4wk	E2 vs E1/C: • Pain Disability Index (+exp2) • EQ-5D (+exp2) • SF-36 (+exp2) • SF-36 (role physical functioning and general health perception) (-) • Visual Analog Scale (-)
Rowbotham et al. (2003) RCT (7) $N_{start\ (stroke\ patients)}$=10 $N_{end\ (stroke\ patients)}$=10 TPS=Chronic	E: High-strength levorphanol C: Low-strength levorphanol Duration: 0.75mg/d (3x/d; with a maximum of 7 tablets at a time), 7d/wk for 8wk OR 0.15mg/d (3x/d; with a maximum of 7 tablets at a time), 7d/wk for 8wk	• Pain Reduction (+exp) • Visual Analog Scale (+exp) • Multidimensional Pain Inventory (-) • Profile of Mood States (-)

Bainton et al. (1992) RCT (5) N_{start}=20 N_{end}=20 TPS=Chronic	E: Naloxone (8mg) C: Saline (20mg) Duration: 8mg (injection) of naloxone 1x/wk for 3wk OR 20mg (injection) of saline 1x/wk for 3wk	• Verbal Rating Scale (-) • Visual Analog Scale (-)
rTMS		
Andre-Obadia et al. (2006) RCT (8) N_{start}=12 N_{end}=12 TPS=Chronic	E1: 20Hz rTMS E2: 1Hz rTMS C: Sham rTMS Duration: 25min/d, 1x/wk for 3wk	E1/C vs E2 • Visual Analog Scale: $(+exp_1,+con)$ E1 vs C • Visual Analog Scale (-)
Lefaucheur et al. (2004) RCT (4) N_{start}=60 N_{end}=52 TPS=Chronic	E: 10Hz rTMS C: Sham rTMS Duration: 20min/d, 1x/wk for 2wk + 1wk of observation	• Visual Analog Scale: % Pain Reduction (+exp)
Lefaucheur et al. (2001a) RCT (5) $N_{stroke\ patients}$=12 $N_{stroke\ patients}$=12 TPS=Chronic	E1: 10Hz rTMS E2: 0.5Hz rTMS C: Sham rTMS Duration: 20min/d, 1x/wk for 2wk + 1wk of observation	• Visual Analog Scale: % Pain Reduction (-)
Lefaucheur et al. (2001b) RCT (3) $N_{stroke\ patients}$=7 $N_{stroke\ patients}$=7 TPS=Chronic	E: rTMS C: Sham rTMS Duration: 20min/d, 1x/wk for 2wk + 1wk of observation	• Visual Analog Scale: % Pain Reduction (+exp)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
$+exp_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group
+con indicates a statistically significant between groups difference at α=0.05 in favour of the control group
- indicates no statistically significant between groups differences at α=0.05

Discussion

The most commonly used medications for central neuropathic pain, such as CPSP, are antidepressants and anticonvulsants. Tricyclic antidepressants have been shown to have a beneficial effect on central pain states (Koppel, 1986; Tourian, 1987). Amitriptyline was shown to reduce pain in CPSP patients compared to placebo, but the benefits were lost at four months (Leijon & Boivie, 1989a). A later study found similar rates of pain in CPSP patients taking amitriptyline and those taking placebo (Lampl et al., 2002). Another antidepressant, duloxetine, also failed to demonstrate significant reductions in pain scores relative to placebo (Vranken et al., 2011).

Anticonvulsants, such as chlorpromazine (Margolis & Gianacol, 1956), phenytoin (Cantor, 1972; Mladinich, 1974), carbamazepine (1989a), and levetiracetam (G.J. Jungehulsing et al., 2013) are reportedly minimally effective in reducing pain and associated with poor tolerability. Pregabalin demonstrated conflicting results: one RCT found it to be more effective than placebo in pain reduction (Vranken et al., 2008), while a larger RCT found them to be similarly effective (Kim et al., 2011). Other anticonvulsants such as lamotrigine (Vestergaard et al., 2001) and gabapentin (Serpell, 2002) have been well tolerated and effective in reducing pain in patients with CPSP.

Narcotic and non-narcotic analgesics generally failed to provide adequate pain relief for CPSP (Nuzzo & Warfield, 1985). Morphine has been reported to be effective but associated with significant adverse effects and a tendency to lose its effectiveness over time (Miley et al., 1978). In fact, an RCT found that intravenous morphine was no more effective than placebo in reducing pain in patients with CPSP (Attal et al., 2002). Levorphanol, an oral opioid, was shown to be

significantly more effective in higher doses than lower doses; however the drug was not compared to placebo or control (Rowbotham et al., 2003). Naloxone, an opioid receptor antagonist, demonstrated no benefit in pain relief relative to saline when delivered intravenously (Bainton et al., 1992).

Various anesthetics have been investigated for treatment of CPSP. Transdermal ketamine demonstrated a greater reduction in pain-related disability than placebo, but the two interventions yielded similar levels of pain reduction (Vranken et al., 2005). Intravenous propofol significantly reduced pain intensity in the short term relative to placebo (Canavero & Bonicalzi, 2004). Both anesthetics were well tolerated and associated with only minimal, mild side effects.

Sympathetic blockade in the form of stellate ganglion and lumbar sympathetic blocks or local venous guanethedine blocks may provide some temporary relief of pain (Loh et al., 1981). In one RCT, diluted bee venom (apitoxin) was found to reduce pain scores significantly more than saline when injected locally during acupuncture of areas with heightened pain (Cho et al., 2013). However, the study included a small sample size and did not compared apitoxin to other more commonly used pharmacological medications for treating CPSP.

In terms of MCS, Lefaucheur et al. (2001b) compared rTMS to sham stimulation in patients with trigeminal neuralgia or CPSP. The authors observed a 30% reduction in pain up to 8 days after the 20-minute rTMS, but not to the end of the 12-day follow-up period; the pain reduction was significantly greater with rTMS than sham stimulation. Another study by the same group compared high- and low-frequency rTMS to sham stimulation in patients with neurogenic pain, including CPSP (Lefaucheur et al., 2001a). The study found that only high-frequency rTMS (10Hz) demonstrated significant reductions in pain, although no between-group statistical comparisons were performed. In a larger study by the same group, rTMS and sham stimulation were compared in patients with pain after stroke, spinal cord injury, brachial plexus injury, or trigeminal neuralgia (Lefaucheur et al., 2004). Both the rTMS and sham groups had a significant decrease in their pain immediately after treatment, but the rTMS group had a significantly greater percent pain reduction. Most recently, Andre-Obadia et al. (2006) compared the effect of high- and low-frequency rTMS to sham stimulation in patients with CPSP or peripheral nerve injury. Both high-frequency rTMS and sham stimulation demonstrated significantly greater pain reduction than low-frequency rTMS, but there was no significant difference between high-frequency and sham stimulation. None of the trials found rTMS to be associated with notable adverse events such as seizure.

Mulla et al. (2015) conducted a systematic review and meta-analysis of RCTs examining both pharmacological and non-pharmacological therapies for CPSP, including anticonvulsants, tricyclic antidepressants, opioid antagonists, rTMS, and electroacupuncture. The review found that none of the RCTs demonstrated benefit for pain reduction or other clinically important outcomes, even in therapies commonly used in practice or recommended in clinical practice guidelines, such as amitriptyline and anticonvulsants. The authors excluded trials with less than two weeks of follow-up, stating that even if these therapies are effective, such short-term benefit is not worthwhile given the chronic nature of CPSP. These findings emphasize the lack of robust evidence on which to base guidelines for the management of CPSP and other related pain conditions.

Conclusions Regarding the Treatment of Central Pain Post Stroke

LoE	PICO statement	Number of RCTs	References
1a	There is conflicting evidence about the effect of **gabapentin/pregabalin** to improve pain reduction when compared to a **placebo**.	3	Kim et al. 2011; Vranken et al. 2008; Serpell et al. 2002
1a	There is conflicting evidence about the effect of **anticonvulsants (e.g. Levitiracetam, Lamotrigine)** to improve pain reduction when compared to a **placebo**.	2	Jungehulsing et al. 2013; Vestergaard et al. 2001
1a	**Amitriptyline** may not have a difference in efficacy for improving pain reduction when compared to **placebo**.	2	Lampl et al. 2002; Leijon & Boivie 1989
1b	**Apitoxin** may improve pain reduction when compared to a **saline control**.	1	Cho et al. 2013
1b	**Duloxetine** may not have a difference in efficacy for improving pain reduction when compared to a **placebo.**	1	Vranken et al. 2011
1b	**High dose ketamine (75mg)** may improve pain reduction when compared to a **lower dose of ketamine (50mg)** or a **placebo**.	1	Vranken et al. 2005
1b	**High strength levorphanol** may improve pain reduction when compared to **low strength levorphanol.**	1	Rowbotham et al. 2003
2	**Naloxone** may not have a difference in efficacy when compared to a **saline control** for improving pain reduction.	1	Bainton et al. 1992
1b	**High frequency rTMS** may produce greater improvements in pain reduction than **sham or low frequency rTMS**.	4	Andre-Obadia et al. 2006; Lefaucher et al. 2004; Lefaucher et al. 2001a; Lefaucher et al. 2001b

- A wide range of pharmacological interventions are available for the treatment of central pain post stroke, including anticonvulsants, antidepressants, anesthetics, and narcotics. However, the majority of these require further research to determine their effectiveness in pain reduction.
- Repetitive transcranial magnetic stimulation may be effective in reducing central pain post stroke when delivered at higher frequencies, although further research is required.

17.8 Fatigue Post Stroke

Fatigue is a subjective term and there is no universally accepted definition (Choi-Kwon & Kim, 2011; Van Eijsden et al., 2012). Abnormal or pathological fatigue has been characterized as a state of general tiredness or weariness unrelated to exertion levels that is usually not ameliorated by rest (De Groot et al., 2003).

A review by Choi-Kwon & Kim (2011) proposed that the predisposing factors to post-stroke fatigue (PSF) be classified into 3 main categories: (1) physiological, including pre-stroke fatigue, functional disability, medical comorbidities, sleep disturbances, nutritional problems, and medication; (2) psycho-cognitive, including depression and cognitive dysfunction; and (3) organic, including damage to particular brain areas with consequent neurochemical alterations due to perfusion deficit in stroke.

17.8.1 Prevalence, Risk, and Consequences of Post-Stroke Fatigue
Estimates of the prevalence of PSF vary widely, from 30-74%, depending on the measure used to assess it and the timing of assessment (Table 17.8.1.1). Many studies demonstrated that the patients continue to experience PSF without much fluctuation over time. There is also evidence that fatigue both increases and decreases in frequency over time post stroke (Duncan et al., 2012).

Table 17.8.1.1 Prevalence of Post-Stroke Fatigue

Prevalence	Range (%)
Admission	51.5% - 58.3%
10 days	59%
1 month	28%
2 months	35%
6 months	23% - 68%
1 year	21% - 74%
1.5 years	33% - 64%
2 years	40%
3 years	58%

The most common type of PSF experienced was reported to be physical fatigue (69.6%), followed by activity-related fatigue (67.9%) and mental fatigue (62.5%) (Muina-Lopez & Guidon, 2013). The presence of PSF was found to restrict participation in various activities including those involving self-care (Miller et al., 2013; Young et al., 2013), which can negatively affect functional recovery especially when comorbid depression exists (Badaru et al., 2013). Higher PSF levels were also significantly associated with lower self-efficacy beliefs (Miller et al., 2013; Muina-Lopez & Guidon, 2013). Moreover, PSF has been shown to be significantly associated with mortality, even after adjusting for age and sex, which may suggest that patients suffering from PSF are at a higher risk of mortality than non-fatigued individuals (Naess & Nyland, 2013).

A variety of risk factors for PSF have been identified: depression, chronic pain, sleep disorders, functional disability, neurological impairment, and certain medications; female sex and older age also emerged as independent predictors of fatigue in predictions models (Feigin et al., 2012; Hoang et al., 2012; Mead et al., 2011). Patients with post-stroke pain were reported to have higher fatigue scores, although pain is not required nor necessarily comorbid with PSF (Tang et al., 2015). Currently, controversy exists as to whether there is a causal relationship between depression and fatigue.

Conclusions Regarding Prevalence of Post-Stroke Fatigue

- Fatigue is a common condition post stroke, although there is variation in reported rates.
- Risk factors for post-stroke fatigue include depression, chronic pain, and sleep disorders; it may be associated with poor recovery.

17.8.2 Treatment of Post-Stroke Fatigue

Treatment of PSF is an often varied or even unmet despite its high prevalence and negative impact on patient outcomes. This situation may be due to variation in its clinical definition and assessment, limited understanding of its pathophysiology, as well as a paucity of effective treatment options. An updated Cochrane review of various interventions for PSF included 12 trials with 708 participants (S. Wu et al., 2015). The authors found no evidence to support any of the studied interventions and noted major methodological limitations including small sample sizes, high risk of bias, and PSF as a secondary outcome (Simiao Wu et al., 2015). Given the lack of high-quality studies, there is inadequate evidence on which to base guidelines or recommendations for initiation of therapy, and so management of PSF will be variable based on clinician experience and case-by-case treatment considerations.

Table 17.8.2.1 Summary of RCTs Evaluating Treatment of Post-Stroke Fatigue

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Pharmacological		
Fengli et al. (2018) RCT (6) N$_{start}$=140 N$_{end}$=140 TPS=Chronic	E: Wuling capsule C: Vitamin C Duration: 3x/d	• Inflammatory cytokines IL-1B and IL-10 (+exp) • Barthel Index (+exp)
Liu et al. (2016) RCT (9) N$_{start}$=64 N$_{end}$=58 TPS=Chronic	E: Astragalus membranaceus C: Placebo Duration: 2.8g (3x/d) of astragalus membranaceus, 7d/wk, for 4wk OR 2.8g (3x/d) of placebo, 7d/wk for 4wk	• Brief Fatigue Index (+exp) • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (+exp)
Johansson et al. (2012) RCT N$_{Stroke\ Patients\ (start)}$=6 N$_{stroke\ patients\ (end)}$=6 TPS=Chronic	E: OSU-6162 C: Placebo Duration: Maximum of 45mg (2x/d), 7d/wk for 4wk of OSU-6162 OR Maximum of 45mg (2x/d), 7d/wk for 4wk of placebo	• Mental Fatigue Scale (+exp)
Antidepressants		
Karaiskos et al. (2012) RCT (5) N$_{start}$=60 N$_{end}$=60 TPS=Chronic	E1: Duloxetine E2: Citalopram E3: Sertraline Duration: 60-120mg/d of Duloxetine, 7d/wk for 12wk OR 20-40mg/d of Citalopram, 7d/wk for 12wk OR 50-200mg/d of Sertraline, 7d/wk for 12wk	• Fatigue Severity Scale (-) • Mini Mental State Examination (-) • Modified Rankin Scale (-) • Hamilton Rating Scale-Depression (-) • Hamilton Rating Scale-Anxiety (-)
Choi-Kwon et al. (2007)	E: Fluoxetine C: Placebo	• Fatigue Severity Scale (-) • Visual Analog Scale (-)

RCT (6) N$_{start}$=83 N$_{end}$=NR TPS=Chronic	Duration: 20mg/d of Fluoxetine, 7d/wk for 12wk OR 20mg/d of Placebo, 7d/wk for 12wk	
Modafinil		
Lilicrap et al. 2018 RCT (6) N$_{start}$=36 N$_{end}$=36 TPS=Chronic *12 month follow-up to Bivard et al. (2017)	E: Modafinil C: Placebo Duration: 200mg modafinil, 7d/wk for 6wk	• No between group comparisons for follow-up
Bivard et al. (2017) RCT (6) N$_{start}$=36 N$_{end}$=36 TPS=Chronic	E: Modafinil C: Placebo Duration: 200mg modafinil, 7d/wk for 6wk	• Multidimensional Fatigue Inventory (+exp) • Stroke-Specific Quality of Life scale (+exp)
Poulsen et al. (2015) RCT (6) N$_{start}$=41 N$_{end}$=36 TPS=Chronic	E: Modafinil C: Placebo Duration: 400mg modafinil, 7d/wk for 12wk OR 400mg placebo, 7d/wk for 12wk	• Multidimensional Fatigue Inventory (-) • Fatigue Severity Scale (+exp) • Stroke Specific Quality of Life Questionnaire (+exp)
Non-Pharmacological		
Clarke et al. (2012) RCT (4) N$_{start}$=19 N$_{end}$=16 TPS=	E: Fatigue management C: General stroke education Duration: 20min/d, 3d/wk for 2wk Statistical Analysis: ANOVA	• Fatigue Severity Scale (-) • SF-36 (-) • Hospital Anxiety and Depression Scale (-) • Visual Analog Scale for Fatigue (-)
Zedlitz et al. (2012) RCT (8) N$_{start}$=73 N$_{end}$=68 TPS=Subacute	E: Cognitive therapy + Graded activity training C: Cognitive therapy Duration: 2hr/d, 1d/wk for 12wk (cognitive therapy) + 2hr/d, 2d/wk for 12wk (graded activity training) Statistical Analysis: ANCOVA	• Checklist Individual Strength – Fatigue (+exp) • Self-Observation List – Fatigue (+exp) • Hospital Anxiety and Depression Scale (-) • Stroke Adapted Sickness Impact Profile (-) • 6-Minute Walk Test (-) • Visual Analog Scale (-)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group

Medications used to treat PSF are often selective monoamine reuptake inhibitors (e.g. dopamine, serotonin, norepinephrine) that can promote wakefulness. OSU-6162 is a partial dopamine receptor agonist that acts as a 'dopaminergic stabilizer'. A crossover RCT by Johnasson et al. (2012) reported that the compound significantly reduced fatigue relative to placebo over the course of four weeks, although only half of the subjects were patients with stroke. Modafinil is an atypical, selective, and weak dopamine reuptake inhibitor designed to treat patients with hypersomnia or narcolepsy. An RCT by Poulsen et al. (2015) found that three months of daily modafinil was significantly more effective than placebo in reducing fatigue as well as improving quality of life.

A variety of antidepressants have also been examined for treatment of PSF. A three-month RCT of fluoxetine, a selective serotonin reuptake inhibitor (SSRIs), demonstrated a similar reduction in fatigue when compared to placebo in patients with significant PSF (Choi-Kwon et al., 2007). Another RCT compared the serotonin-norepinephrine reuptake inhibitor duloxetine to two SSRIs, sertraline and citalopram, over the course of three months (Karaiskos et al., 2012). The authors

found that none of the medications significantly reduced fatigue over time, and there were no significant differences between groups.

Three RCTs were identified that investigated the effectiveness of non-pharmacological therapies for reducing PSF. A combination of cognitive therapy and graded activity training was found to improve PSF when compared to cognitive therapy alone (Zedlitz et al., 2012). However, participation in a fatigue management group was as effective as receiving general education regarding PSF (Clarke et al., 2012). Mindfulness-based stress reduction demonstrated significant reductions in PSF, although the control group received no active treatment (B. Johansson et al., 2012).

Astragalus membranaceus is an herb often used traditional Chinese medicine to treat fatigue. In a one-month RCT, the herb significant reduced PSF when compared to placebo (Liu et al., 2016). However, the reduction was no longer significantly different between groups at three-month follow-up. Future research is encouraged to investigate other pharmacological treatment options that may be effective in reducing other symptoms such as depression and pain, which are often comorbid to PSF.

Conclusions Regarding Treatment of Post-Stroke Fatigue

LoE	PICO statement	Number of RCTs	References
1b	**Wuling capsule** may produce greater improvements in inflammatory cytokine expression and activities of daily living when compared to **vitamin C**.	1	Fengli et al. 2018
1b	**Astragalus membranaceus** may produce greater improvements in fatigue and quality of life when compared to a **placebo**.	1	Liu et al. 2016
1b	**OSU-6162** may produce greater improvements in mental fatigue exertion when compared to a **placebo**.	1	Johansson et al. 2012
1b	**Antidepressants** may not have a difference in efficacy for improving fatigue when compared to a **placebo or other antidepressants.**	2	Karaiskos et al. 2012; Choi-Kwon et al. 2007
1a	There is conflicting evidence about the effect of **Modafinil** to improve fatigue when compared to a **placebo**.	2	Bivard et al. 2017; Poulsen et al. 2015
2	**Fatigue-specific management programs** may not have a difference in efficacy when compared to a **general stroke education programs** for improving fatigue.	1	Clarke et al. 2012
1b	**Cognitive behavioural therapy with graded activity training** may produce greater improvements in fatigue than **cognitive behavioural therapy on its own**.	1	Zedlitz et al. 2012

- Limited evidence shows that Wuling capsule, Astragalus mebranaceus, OSU-6162 and cognitive behavioural therapy with graded activity training may be effective treatments for post-stroke fatigue.
- While antidepressants may not be effective treatments.
- The literature is mixed on the use of Modafinil for treating post-stroke fatigue.

17.9 Insomnia Post Stroke

There is limited research on the prevalence of post-stroke insomnia, although some research does suggest sleep disturbance following stroke (Suh et al., 2014). Post-stroke insomnia (PSI) may occur concurrently with or independent of depression, and it may be more common in patients with cortical lesions compared to other lesions (Suh et al., 2014).

Table 17.9.1 Summary of RCTs Evaluating Treatment for Post-Stroke Insomnia

Authors (Year) Study Design (PEDro Score) Sample Size$_{start}$ Sample Size$_{end}$ Time post stroke category	Interventions Duration: Session length, frequency per week for total number of weeks	Outcome Measures Result (direction of effect)
Cai et al. (2015) RCT (5) N$_{start}$=154 N$_{end}$=NR TPS=Subacute	E: Auricular acupuncture (specialized plaster placed on ear acupoints) + Music therapy C: Auricular acupuncture (specialized plaster placed on ear acupoints) Duration: 60s (3x/d), 5d/wk for 4wk + 30min/d, 5d/wk for 4wk	• Insomnia alleviation rate (+exp)
Lee et al. (2009) RCT (7) N$_{start}$=60 N$_{end}$=52 TPS=Chronic	E: Intradermal acupuncture C: Sham acupuncture Duration: *Not Reported*	• Insomnia Severity Index (+exp) • Athens Insomnia Scale (+exp) • Blood Pressure (-)
Kim et al. (2004) RCT (7) N$_{start}$=32 N$_{end}$=30 TPS=Chronic	E: Intradermal acupuncture C: Sham acupuncture Duration: 25min/d (4 needles on 4 acupoints), 2d/wk for 1wk	• Insomnia Severity Index (+exp) • Athens Insomnia Scale (+exp) • Morning Questionnaire (+exp)

Abbreviations and table notes: C=control group; D=days; E=experimental group; H=hours; Min=minutes; RCT=randomized controlled trial; TPS=time post stroke category (Acute: less than 30 days, Subacute: more than 1 month but less than 6 months, Chronic: over 6 months); Wk=weeks.
+exp indicates a statistically significant between groups difference at α=0.05 in favour of the experimental group
+exp$_2$ indicates a statistically significant between groups difference at α=0.05 in favour of the second experimental group

Discussion

Two studies have compared the effects of intradermal acupuncture to sham acupuncture in treating PSI (Kim et al., 2004; Lee et al., 2009). Kim et al. (2004) reported that patients in the treatment group demonstrated a statistically significant improvement in sleep compared to the control group as measured by the Morning Questionnaire, Insomnia Severity Index, and Athens Insomnia Scale. Similarly, Lee et al. (2009) reported significant improvements with treatment relative to control on the latter two scales. More recently, Cai et al. (2015) reported that a combination of auricular acupuncture and music therapy was more effective in reducing symptoms of insomnia than acupuncture alone. Acupuncture is generally deemed to be safer than medications such as benzodiazepines because of adverse effects associated with sedatives. As well, intradermal acupuncture is thought to be more effective at stimulating acupoints compared to conventional acupuncture (Kim et al., 2004). Additional high-quality RCTs with large sample sizes are required to determine the effectiveness of acupuncture in treating PSI.

Conclusions Regarding Treatment of Post-Stroke Insomnia

LoE	PICO statement	Number of RCTs	References
2	**Acupuncture combined with music therapy** may produce greater improvements in insomnia alleviation when compared to a **sham treatment**.	1	Cai et al. 2015
1a	**Intradermal acupuncture** may produce greater improvements in insomnia severity when compared to a **sham treatment**.	2	Lee et al. 2009; Kim et al. 2004

- Acupuncture may be an effective treatment for insomnia post stroke, although further research is required.

Summary

Bladder Dysfunction

1. *There is Level 1a evidence that pelvic floor training improves muscle control and reduces urinary incontinence when compared to standard care, but there is conflicting Level 1b evidence as to whether it improves health-related quality of life.*

2. *There is Level 1a evidence that traditional Chinese medicines reduce urinary incontinence but do not improve functional outcomes.*

3. *There is Level 1b evidence that transcutaneous electrical nerve stimulation reduces urinary incontinence when compared to no treatment, and that stimulation is more effective at 20Hz than 75Hz.*

4. *There is Level 1b evidence that the time of day for catheter removal does not impact subsequent urinary incontinence.*

5. *There is limited Level 2 evidence that a functionally-oriented rehabilitation program reduces urinary incontinence and improves wellbeing when compared to a conventional Bobath approach.*

6. *There is limited Level 2 evidence that bladder reconditioning prior to catheter removal does not impact subsequent urinary incontinence.*

7. *There is limited Level 3 evidence that indwelling urinary catheters are associated with worse outcomes, including urinary tract infections.*

Bowel Dysfunction

1. *There is Level 1b evidence that a nursing program consisting of an assessment, educational material, diagnostic results, and treatment recommendations reduce constipation and fecal incontinence post stroke when compared to routine care.*

2. *There is Level 1b evidence that a traditional Japanese medicine, Diakenchuto, reduces constipation post stroke when compared to routine care.*

3. *There is Level 1b evidence that a protocol of tui-pushing and point sticking reduces constipation post stroke when compared to routine care.*

Venous Thromboembolism

1. *There is limited Level 2 evidence that bowel training is most efficient when coinciding with previous bowel regimens, but schedule of suppository use did not have an effect.*

2. *There is conflicting Level 1a evidence as to whether low molecular weight heparin is more effective than unfractionated heparin, aspirin, or placebo in reducing the incidence of deep vein thrombosis, without increasing the risk of bleeding complications.*

3. *There is Level 2 evidence that unfractionated heparin reduces the incidence of deep vein thrombosis when compared to placebo.*

4. *There is Level 2 evidence that unfractionated heparin is no more effective than intermittent pneumatic compression or neuromuscular electrical stimulation in reducing the incidence of deep vein thrombosis.*

5. *There is Level 1a evidence that intermittent pneumatic compression reduces the incidence of deep vein thrombosis when compared to standard care, although there is limited Level 2 evidence that suggests otherwise.*

6. *There is Level 1a evidence that graded compression stockings are no more effective than standard care in reducing the incidence of deep vein thrombosis post stroke.*

7. *There is Level 1b evidence that thigh-high graded compression stockings reduce the incidence of deep vein thrombosis when compared to below-knee stockings.*

Seizures

1. *There is Level 1b and Level 2 evidence that lamotrigine, gabapentin, and carbamazepine are similar in reducing the rate of recurrent post-stroke seizures, but carbamazepine is more poorly tolerated.*

2. *There is Level 1b evidence that valproic acid does not prevent post-stroke seizures when compared to placebo, but may confer neuroprotective effects.*

Osteoporosis

1. *There is Level 1a evidence that bisphosphonates preserve bone mineral density post stroke when compared to placebo, although there is limited Level 2 evidence that suggests otherwise.*

2. *There is Level 1b evidence that vitamin D preserves bone resorption and reduces the rate of fractures when compared to placebo.*

3. *There is Level 1b evidence that vitamin B does not reduce the rate of fractures when compared to placebo.*

4. *There is limited Level 2 evidence that vitamin K preserves bone mineral density and enhances bone metabolism when compared to no treatment.*

5. *There is limited Level 2 evidence that calcitonin does not enhance bone metabolism when compared to placebo.*

Central Pain

1. *There is Level 1b evidence that lamotrigine reduces central pain post stroke when compared to placebo.*

2. *There is Level 1b evidence that gabapentin reduces central pain post stroke when compared to placebo.*

3. *There is Level 1b evidence that propofol reduces central pain post stroke when compared to placebo.*

4. *There is Level 1b evidence that high-dose levorphanol is more effective than low-dose Levorphanol in reducing central pain post stroke.*

5. *There is Level 1b evidence that apitoxin is more effective than saline during acupuncture in reducing central pain post stroke.*

6. *There is Level 1b evidence that levetiracetam is no more effective than placebo in reducing central pain post stroke.*

7. *There is Level 1b evidence that carbamazepine is no more effective than placebo in reducing central pain post stroke.*

8. *There is Level 1b evidence that duloxetine is no more effective than placebo in reducing central pain post stroke.*

9. *There is Level 1b evidence that ketamine is no more effective than placebo in reducing central pain post stroke.*

10. *There is Level 1b evidence that morphine is no more effective than placebo in reducing central pain post stroke.*

11. *There is Level 1b and Level 2 evidence that high-frequency repetitive transcranial magnetic stimulation is more effective than low-frequency stimulation in reducing central pain post stroke.*

12. *There is Level 2 evidence that naloxone is no more effective than placebo in reducing central pain post stroke.*

13. *There is conflicting Level 1b evidence as to whether pregabalin is more effective than placebo in reducing central pain post stroke.*

14. *There is conflicting Level 1b evidence as to whether amitriptyline is more effective than placebo in reducing central pain post stroke.*

15. *There is conflicting Level 1b and Level 2 evidence as to whether repetitive transcranial magnetic stimulation is more effective than sham stimulation in reducing central pain post stroke.*

Fatigue

1. *There is Level 1b evidence that modafinil reduces fatigue post stroke when compared to placebo.*

2. *There is Level 1b evidence that OSU-6162 reduces fatigue post stroke when compared to placebo.*

3. *There is Level 1b evidence that a combination of cognitive therapy and graded activity training reduced fatigue post stroke when compared to cognitive therapy alone.*

4. *There is Level 1b evidence that astragalus membranaceus, a traditional Chinese herbal medicine, yields a short-term reduction in fatigue post stroke when compared to placebo.*

5. *There is Level 1b and Level 2 evidence that antidepressants do not reduce fatigue post stroke.*

6. *There is Level 2 evidence that mindfulness-based stress reduction reduces fatigue post stroke when compared to no therapy.*

7. *There is Level 2 evidence that a fatigue management program does not reduce fatigue post stroke when compared to a stroke education program.*

Insomnia

1. *There is Level 1a evidence that intradermal acupuncture reduces insomnia when compared to sham acupuncture.*

2. *There is Level 1b that acupuncture combined with music therapy reduces insomnia when compared to acupuncture alone.*

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