Abstract

Medical issues post stroke are those which are within the domain of the doctor and the nurses, but are unrelated to secondary stroke prevention. Not only do these complications occur relatively frequently, but they have also been shown to contribute to poor outcome. As such, an understanding of these disorders is critically important to stroke care and management. Although the number of potential medical complications is extensive, this review will focus on six of the most common and clinically relevant: urinary and fecal incontinence, venous thromboembolism, seizures, osteoporosis, central pain states, and post-stroke fatigue. Both short-term and long-term complications will be evaluated.
Key Points

Urinary Incontinence
- The treatment of urinary/fecal incontinence post stroke has not been well studied.
- Indwelling urinary catheters should only be used for cases of intractable urinary retention, continuous wetness or the need for monitoring.
- Prompted voiding and biofeedback-assisted pelvic training plus behavioral therapy and weekly in-home visits reduce incontinent episodes. Treatment with a functionally oriented rehabilitation approach vs. a Bobath approach for urinary incontinence post stroke has not been well studied.

Deep Vein Thrombosis
- The incidence of DVT is less than 10% in the rehabilitation phase.
- Anticoagulation reduces the incidence of DVT. Low molecular-weight heparin is more effective than unfractionated heparin. The use of physical methods does not appear to be effective in preventing DVT.

Seizures
- The prevalence/incidence of seizures varies, on average approximately 10% of stroke patients experience seizures.
- The treatment of seizures post stroke has not been well studied. There is no significant difference in the efficacy of any antiepileptic in the management of post stroke seizure.

Osteoporosis
- Ipiflavone, vitamin D along with calcium supplementation, sunlight therapy, a combination of vitamin B12 and folate, and bisphosphonates can all be used to reduce the risk of osteoporosis post stroke.

Central Pain State
- Central pain states post stroke are uncommon, but not rare.
- The majority of pain states do not respond well to treatment, although a broad range of drug treatments are available.

Post-stroke Fatigue
- Post-stroke fatigue is relatively common. A limited number of treatments have been evaluated. Cognitive therapy, especially when augmented with graded activity training has proven to be useful.
- At present there is no evidence to support the effectiveness of pharmacological treatment for post-stroke fatigue.
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17. Medical Complications Following Stroke

17.1 Type and Frequency of Medical Complications Post Stroke

Medical issues post stroke are those unrelated to secondary stroke prevention and have to do with those disorders, which are the domain of the doctor and the nurses. Although the number of potential medical complications is extensive, this review will focus on five of the most common and clinically relevant and include both short-term and long-term complications: urinary incontinence, venous thromboembolism, seizures, osteoporosis and central pain states. Not only do these complications occur relatively frequently, but they have also been shown to contribute to poor outcome (Doshi et al. 2003). Complications tend to occur more frequently among older patients and those suffering from more severe strokes (Davenport et al. 1996). Reports of the percentages of patients experiencing one or more medical complications vary widely (44-95%) (McLean 2004). Table 17.1 reports the incidence of several medical complications associated with stroke rehabilitation.

The development of medical complications in acute care may result in a delayed transfer to inpatient rehabilitation. Roth et al. (2007) reported that among a cohort of 2,457 consecutively admitted patients, medical complications as a group, accounted for 17.3% of the variance in a model examining factors associated with the time (days) to rehab following stroke onset. Pneumonia and and urinary tract infections were the most significant medical factors responsible for delay.

Table 17.1 Frequency of Medical Complications During Inpatient Stroke Rehabilitation

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Design (n)</th>
<th>Complication/Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dromerick &amp; Reding (1994)</td>
<td>Retrospective (n=100)</td>
<td>Urinary tract infection (44%) Pain (31%) Pneumonia (7%) Falls (25%) Pulmonary embolus (0%)</td>
</tr>
<tr>
<td>Kalra et al. (1995)</td>
<td>Prospective (n=245)</td>
<td>Urinary tract infection (25%) Chest infections (11.8%) DVT (4.9%) Depression (31%) Seizures (3.6%) Central pain (&lt;1%)</td>
</tr>
<tr>
<td>Davenport et al. (1996)</td>
<td>Prospective (n=613)</td>
<td>Falls (22%) Urinary tract infection (16%) Chest infections (12%)</td>
</tr>
<tr>
<td>Johnston et al. (1998) RANITTAS Trial</td>
<td>Prospective (n=279)</td>
<td>Urinary tract infection (11%) Pneumonia (10%) Deep vein thrombosis (2%) Seizure (3%)</td>
</tr>
<tr>
<td>Roth et al. (2001)</td>
<td>Prospective (n=1,029)</td>
<td>Urinary tract infections (30.5%) Deep vein thrombosis (4.1%) Pulmonary embolism (1.1%) Seizures (1.5%)</td>
</tr>
<tr>
<td>Langhorne et al. (2000)</td>
<td>Prospective (n=311)</td>
<td>Urinary tract infection (24%) Chest infection (n=22%) Pain (34%) Pressure sore (21%)</td>
</tr>
</tbody>
</table>
Roth et al. (2001) reported that 75% of rehabilitating stroke patients experienced at least one medical complication during their inpatient hospital stay. Urinary tract infections, soft tissue pain, depression, falls and elevated blood pressure were the most common complications and resulted in transfer back to acute care on occasion (19%). Patients most likely to experience a complication post stroke were those with greater severity of stroke, hypoalbuminemia and a history of hypertension. Hung et al. (2005) reported that 44% of patients transferred for inpatient rehabilitation experienced at least one medical complication. Three percent of patients required transfer back to the acute care hospital. Kalra et al. (1995) reported that patients admitted for specialized stroke rehabilitation had fewer chest infections, episodes of aspiration, urinary tract infections, and musculoskeletal pain compared with patients admitted to general wards.

17.2 Urinary Dysfunction Following Stroke

17.2.1 Disorders of Voiding

The most frequently occurring voiding abnormalities associated with stroke have been identified as urinary frequency, urge incontinence and urinary retention (Marinkovic & Badlani 2001). There have been reports that 21%-47% of stroke patients experience urinary retention (Burney et al. 1996; Doshi et al. 2003). The commonality and the importance/necessity for clinicians to address and manage these complications have been highlighted by three recent review articles on overactive bladder, urinary incontinence, and voiding dysfunctions in stroke patients, respectively (Linsenmeyer 2012; McKenzie & Badlani 2012; Mehdi et al. 2013).
17.2.2 Prevalence of Urinary Incontinence

Urinary incontinence (UI) is a common problem following a stroke with reported incidences ranging from 30% to 79% (Brittain et al. 1999; Sreeraj et al. 2012; van Kuijk et al. 2001). The discrepancies in the reported rates likely arise from differing definitions of incontinence, the timing of UI measurement, and the populations under study.

Urinary incontinence is common among the elderly, particularly women (Brooks 2004). Estimates of UI in women are believed to be 1.3 to 4.5 times greater compared with men (Jorgensen et al. 2005). The prevalence of any symptoms of UI among elderly women ranges from 10% to 40% depending on variations in definitions and survey methods. However, the prevalence of severe incontinence is much lower (4% to 8%). Among women, stroke may exacerbate existing stress incontinence (Brooks 2004).

Incontinence post stroke often resolves spontaneously (without treatment) in eight weeks (Borrie et al. 1986; Brocklehurst et al. 1985). It has been reported that as great as 60% of stroke victims have UI (Borrie et al. 1986; Brocklehurst et al. 1985; Nakayama et al. 1997), however of this percentage, 17%-22% will have premorbid UI (Benbow et al. 1991; Borrie et al. 1986), and 14%-19% will have persisting incontinence (Barer 1989; Nakayama et al. 1997) at six months. Patients who experience severe strokes are those that tend to have the greatest difficulty with incontinence (Nazarko 2003). Brittain et al. (1999) noted that non-neurological factors such as pre-morbid incontinence or stroke-related impairments, such as motor weakness, altered level of consciousness, cognitive impairment, ataxia and sensory lesions, in the presence of otherwise normal bladder function can contribute to the increase in incontinence. Normal age-related changes in bladder function may also independently affect recovery (Marinkovic & Badlani 2001). Jorgensen et al. (2005) identified depression, motor leg function and cognitive impairment as risk factors for incontinence. Gariballa (2003) found that patients with UI at admission tended to be more undernourished and dehydrated, more impaired, at greater risk for infective complications, and older then patients without UI.

A study of 935 acute stroke patients demonstrated that significant risk factors for post stroke UI included age, severity of stroke, 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. 2001). Bean et al. (2003) noted an almost 2-fold difference in level of disability post-stroke among those who were incontinent versus those who were continent (p<0.001). One study found that patients suffering from UI on admission often 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 long-term poor prognosis for functional recovery. As Forster and Young (2002) note, “treatment evidence specific to stroke is limited”.

Kolominsky-Rabas et al. (2003) examined the occurrence of UI and the long-term effect UI had on subjects’ prognosis and institutional status following stroke 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 sub acute stage of stroke. Although the time since stroke onset was not stated, Brittain et al. (2000) reported that a significantly higher proportion of community-dwelling persons 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 age and sex differences between the groups. Stroke survivors were 1.77 times more likely to experience urinary symptoms than non-stroke persons. More stroke survivors reported a significant impact on lifestyle than did the non-stroke subjects. Twice as many stroke survivors than non-stroke persons reported that their urinary symptoms were moderate to severe.

Jorgensen et al. (2005) reported that among a sample of 242 community-dwelling stroke survivors, 17% were incontinent compared with a non-stroke control group, where the prevalence was 7%. The study tracked subjects an average of nine years post stroke. UI was associated with depression, poor leg motor function and impaired cognition. Williams et al. (2012) reported that increasing age, female sex, pre-stroke urinary incontinence and severe stroke were independent predictors of UI at 12 months. It is important to note that 14.3% of patients in this population study had pre-stroke UI.

Table 17.3 The Prevalence of Urinary Incontinence Following Stroke

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Prevalence and Timing of Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brocklehurst et al. (1985)</td>
<td>135</td>
<td>39% at admission; 25% at 6 months; 15% at 1 year; 23% at 2 years</td>
</tr>
<tr>
<td>Wade et al. (1985)</td>
<td>532</td>
<td>44% at admission</td>
</tr>
<tr>
<td>Borrie et al. (1986)</td>
<td>151</td>
<td>60% at admission; 29% at 3 months</td>
</tr>
<tr>
<td>Fullerton et al. (1988)</td>
<td>205</td>
<td>64% at admission</td>
</tr>
<tr>
<td>Ween et al. (1996)</td>
<td>432</td>
<td>41% at 2 weeks</td>
</tr>
<tr>
<td>Kalra et al. (1993)</td>
<td>96</td>
<td>79% at admission</td>
</tr>
<tr>
<td>Nakayama et al. (1997)</td>
<td>935</td>
<td>47% at admission; 28% at discharge; 19% at 6 months.</td>
</tr>
<tr>
<td>Brittain et al. (2000)</td>
<td>423</td>
<td>64% among community-dwelling (32% among non-stroke controls)</td>
</tr>
<tr>
<td>Patel et al. (2001)</td>
<td>235</td>
<td>40% at admission; 19% at 3 months; 15% at 1 year; 10% at 2 years</td>
</tr>
<tr>
<td>Pandya et al. (2002)</td>
<td>204</td>
<td>51% at admission</td>
</tr>
<tr>
<td>Kolominsky-Rabas et al. (2003)</td>
<td>752</td>
<td>41% at admission</td>
</tr>
<tr>
<td>Jorgensen et al. (2005)</td>
<td>242</td>
<td>17% at 9 yrs (community-dwelling) (7% among non-stroke controls)</td>
</tr>
<tr>
<td>Ersoz et al. (2007)</td>
<td>110</td>
<td>27% at an average of 6 months</td>
</tr>
<tr>
<td>Wilson et al. (2008)</td>
<td>~22K</td>
<td>42-44% at week 2, 15-20% at discharge</td>
</tr>
<tr>
<td>Kovindha et al. (2009)</td>
<td>185</td>
<td>12.4% at admission, 8.1% at discharge</td>
</tr>
<tr>
<td>Williams et al. (2012)</td>
<td>340</td>
<td>43.5% at 3 months, 37.7% at 12 months</td>
</tr>
<tr>
<td>Sreeraj et al., (2012)</td>
<td>486</td>
<td>29.4% at admission</td>
</tr>
</tbody>
</table>

Gelber et al. (1993) suggested that three mechanisms were responsible for incontinence post stroke (van Kuijk et al. 2001). These included:

- Urge incontinence and bladder hyperreflexia from disrupted neuromicturition pathways.
Incontinence from stroke-related motor, cognitive and language deficits, despite normal bladder function.

Overflow incontinence and bladder hyporeflexia from concurrent neuropathy or from the concurrent medications, unrelated to the acute stroke.

In (2013), Mehdi et al. built upon Gelber et al. (1993) suggestions and expanded the number of causes and types of urinary incontinence after stroke to include:

- **Detrusor hyperreflexia & urge incontinence:**
  - Due to indirect damage to the neuromicturition pathways
  - Involuntary leakage of urine accompanied or preceded by urgency

- **Detrusor hyporeflexia & overflow incontinence:**
  - Due to initial loss of bladder tone and non-stroke factors
  - Dribbling and/or continuous leakage of urine associated with incomplete bladder emptying and urinary retention

- **Impaired awareness urinary incontinence:**
  - Reduced ability to be aware of bladder signals before leakage, to take notice of eventual leakage, or both

- **Functional incontinence:**
  - Communicative, cognitive, and mobility difficulties leading to UI despite normal bladder function

- **Stress incontinence:**
  - Not directly caused by stroke but a pre-existing problem may be exacerbated

- **Transient cause of urinary incontinence:**
  - Reversible causes such as medications, urinary tract infections, fecal impaction and delirium

**Normal Bladder Function**
Bladder (detrusor) and urethral functions are coordinated for the storage and emptying of urine (Borrie 1998). This involves areas of the central nervous system and multiple peripheral nervous systems as listed below:

- Sympathetic nervous system relaxes the detrusor muscle while internal urethral sphincter control is maintained by sympathetic alpha-adrenoceptors
- Parasympathetic acetylcholine receptors mediate detrusor contracture.
- Somatic (voluntary) nervous system innervates the pelvic floor muscles, including the external urethral sphincter.
- A micturition centre in the brainstem (pons) informs when the bladder is filling and controls the sacral reflex when bladder filling reaches a certain level.
- The micturition centre in the frontal lobes provides conscious input to the pontine micturition centre allowing the inhibition of urination until the time of voluntary control.
- Normally, we are unaware of bladder fullness until a capacity of about 300 cc is reached. The need to void is then inhibited or controlled by the frontal lobes.

**Pathophysiology of Incontinence Post Stroke**
A stroke can contribute to incontinence by affecting the frontal lobe or pontine micturition centres. Two problems can arise. The most common is detrusor hyperflexia where the stroke survivor is aware of the need to pass urine but cannot inhibit bladder contraction as well (Nazarko 2003). This results in
frequency, urgency and possible urge incontinence (Fader & Craggs 2003; Nazarko 2003). The second problem is one of incomplete bladder emptying (urinary retention) (Fader & Craggs 2003).

**Detrusor Hyperreflexia**

Cortical and subcortical strokes generally result in an unstable or hyperactive detrusor (Borrie 1998). Borrie (1998) has noted that unstable detrusor contractions occur with little warning and result in symptoms of urinary urge incontinence. The bladder volume at which this occurs can be variable but it is usually lower than the volume at which a person with a normally functioning bladder would normally have a strong urge to void. Borrie (1998) also notes that detrusor hyperreflexia is not inevitable following a stroke. It has been noted that UI is more common with larger strokes with a greater number of accompanying deficits and is closely associated with bowel incontinence, dysphagia and overall functional level, all markers of more severe strokes. A recent urodynamic study in stroke patients with UI showed differences in detrusor activity (over versus under) dependent on time since stroke (Chou et al. 2013). Urodynamic pathologies in the early stage post stroke (up to 2 months) were identified as detrusor underactivity with a non-relaxing sphincter, where as the urodynamics in the later stages (> 2 months post stroke) related more frequently to detrusor overactivity and dyssynergic urethral sphincters.

**Urinary Retention**

In the initial stages of a stroke, acute urinary retention is commonly seen. However, urinary retention is not commonly seen by the time a patient enters rehabilitation. Detrusor sphincter dyssynergia, a problem seen in spinal cord injured patients occurs when the urethral sphincter fails to relax as the bladder contracts, resulting in incomplete bladder emptying (Fader & Craggs 2003; Nazarko 2003). Incomplete bladder emptying with significant residual urine is a significant risk factor for the development of urinary tract infections.

To determine if complete bladder emptying is occurring, a true void residual urine test, or post-void residual urine (PVR) volume, must be collected. Intermittent (in/out) catheterization is considered the gold standard measure for obtaining a PVR volume, but portable bladder ultrasound devices offer an alternative means that is practical, non-invasive, and cost-effective (Chan 1993). Two consecutive PVR volumes > 150mL are indicative of incomplete bladder emptying (Borrie 1998). There is no consensus regarding what volume of PVR is considered abnormal (Grosshans et al. 1993), overall the general consensus is that a PVR > 150mL be viewed as abnormal (based to some degree on the volume of urine voided before catheterization)(Borrie 1998).

One study has been conducted and looked at the effectiveness of a standardized bladder scan protocol for using portable ultrasound devices to measure PVR in stroke patients (Kim et al. 2012). Two separate protocols were developed, each dependent on whether or not the patient could urinate volitionally. Overall, the standardized scan protocol demonstrated positive implications for effectively managing urinary retention post stroke, specifically, in terms of appropriate times to catheterize and to scan for PVR volumes.

**Other Factors**

Several pieces of literature have shed light on post stroke continence being a consequence of factors beyond those relating to neurological deficits, including factors such as immobility and dependency (Fader & Craggs 2003; Linsenmeyer 2012; Nazarko 2003). A number of factors which can affect continence, following a stroke but are often overlooked. Such factors include:

- Communication difficulties, particularly an inability to communicate voiding needs.
• Mobility problems, such as hemiplegia make some patients dependent on caregivers to void in a socially appropriate manner. Lack of caregiver support may also make it difficult to toilet the stroke patients quickly enough.
• Post stroke depression and confusion may result in a failure to communicate the need for assistance.
• Medications, such as diuretics can increase the frequency of the need to void; others can increase confusion, while still others such as antihypertensives may affect the autonomic nervous system leading to retention.

Table 17.4 Diagnosis of Various Bladder Dysfunction (from Borrie 1998)

<table>
<thead>
<tr>
<th>History</th>
<th>Finding that May be Present</th>
<th>Residual</th>
<th>Pathophysiology Confirmed by Urodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency</td>
<td>Signs consistent with specific neurological disease</td>
<td>Low</td>
<td>Detrusor instability</td>
</tr>
<tr>
<td>Stress</td>
<td>Demonstrated during stress</td>
<td>Low</td>
<td>(Genuine) stress incontinence</td>
</tr>
<tr>
<td>Overflowing/incomplete emptying</td>
<td>Palpable bladder, Enlarged prostate, Urethral stricture, Reduced anal sphincter tone, Reduced anal sensation</td>
<td>High</td>
<td>Outlet obstruction and/or poorly contractile detrusor</td>
</tr>
<tr>
<td>Mixed</td>
<td>Variable</td>
<td>Variable</td>
<td>Mixed</td>
</tr>
<tr>
<td>Functional</td>
<td>Impaired mobility, Impaired mental state, Environmental factors</td>
<td>Low</td>
<td>Functional</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Drugs, Restraints</td>
<td>Variable</td>
<td>Iatrogenic</td>
</tr>
</tbody>
</table>

**Urinary Tract Infection**

Urinary tract infections (UTI) are the most commonly encountered medical complication associated with stroke rehabilitation (Roth et al. 2001). Several factors have been identified as predisposing risk factors of UTI post-stroke, including: age (> 65 year), sex (female), a history of UI, prior stroke, stroke syndrome, use of β-Block or antidepressants, a post void residual (PVR) of 150 mL, and catheterization (Dromerick & Edwards 2003; Ifejika-Jones et al. 2013; Sabanathan et al. 1985). Ifejika-Jones et al. (2013) examined the impact of hospital-acquired symptomatic urinary tract infection (SUTI) in stroke patients and how SUTI affected patients discharge disposition. Patients with an SUTI were 57% less likely to be discharged home, as opposed to an inpatient rehabilitation, skilled nursing facility, or long-term acute care facility.

**17.2.3 Treatment of Urinary Incontinence Post Stroke**

**Management of Urinary Incontinence**

There are few RCTs evaluating the efficacy of bladder management to treat urinary incontinence post stroke, although the issue has been studied in other patient populations. The choice will often be dictated by the stroke patient’s type of incontinence. In the absence of rigorous evidence, Borrie (1998) notes that a stepwise approach is best, beginning with behaviour intervention, progression to medication only when needed and considering surgical interventions only as a desperate last resort.

A recent Cochrane review (Thomas et al. 2008) investigating optimal methods for prevention and treatment of urinary incontinence after stroke in adults included the results from 12 trials (n=724). There was a wide range of interventions including behavioural interventions (timed voiding, pelvic floor
muscles training), specialized professional input interventions (continence nurse practitioner care), complementary therapy interventions (acupuncture, moxibustion), pharmacotherapy (estrogen, oxybutynin, meclofenoxate) and physical therapy (sensory-motor feedback combined with timed voiding). A pooled analysis across all interventions combined was not performed. Two trials (Brittain et al. 2000; Wikander et al. 1998) offered some evidence supporting the use of input from specialized professionals using systematic methods to help evaluate, manage, and improve outcome of patients with continence complications. One trial (Brittain et al. 2000) suggested short-term and even long-term improvements in symptoms of urinary incontinence could be established through individualized care. While complementary interventions appeared to be effective compared with the placebo condition, small sample sizes and limited reporting of methodological details reduce the generalizability of the findings. While estrogen therapy was effective in reducing the number of incontinence episodes in a week, the therapy is generally contraindicated following stroke. There is limited evidence suggesting that the acute stage of rehabilitation has the largest impact on urinary incontinence following stroke. However, there is a paucity of evidence from studies done with stroke patients that helps direct specific practice guidelines. The authors concluded that further research is required.

Dumoulin et al. (2005) conducted a systematic review investigating the benefits of behavioural therapies used to treat urinary incontinence. The study included only four RCTs, a single cohort study and recommendations from three clinical practice guidelines. This study found limited evidence for the reduction of UI in male stroke patients using combination treatment including bladder retraining with urge suppression and pelvic floor exercises. The authors concluded that although there is increasing recognition of the benefits of using behavioral approaches as treatment for stroke patients with a high occurrence of continual UI, the evidence remains very limited for specific treatments used for stroke survivors with UI.

**Fluid Intake**

The total measurable fluid intake should be approximately 1500 – 1800 mL per 24 hours. The use of intravenous fluids or a feeding tube may result in fluid loads greater than 2L per day, which will in turn compromise bladder continence (Borrie 1998).

**Bladder Training**

Scheduled voiding programs follow a set schedule of voiding every 2-4 hours regardless of whether the patient “needs to go” because post stroke cortical awareness of bladder fullness is often reduced (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. Bladder training allows for lengthening of the voiding interval as the patient becomes consistently dry (Borrie 1998; Burgio & Burgio 1986). However, Duncan et al. (2005) suggest that there is no evidence for or against a scheduled voiding program. These authors recommend an individualized bladder training program and the use of prompted voiding for incontinent stroke patients.

**Pharmacological Treatments**

Borrie (1998) has noted that drug therapy should be implemented only after an adequate trial of behavioural interventions. Drugs, particularly in the elderly, often have significant side-effects. Borrie has noted that post stroke detrusor hyperflexias treated with drugs with various degrees of anticholinergic medications. These medications include Flavoxate, oxybutynin, propantheline and imipramine. These drugs should be started at a low dose and increased gradually over days, if not weeks.
Borrie (1998) has noted that **Flavoxate** is often worth trying initially because its direct smooth muscle action and limited cholinergic effect leads to fewer adverse side effects. **Oxybutynin** is an anticholinergic which is frequently used. **Propantheline** supposedly does not cross the blood-brain barrier, with a theoretical advantage over other drugs which can lead to confusion. **Tolterodine** is another anticholinergic which is said to have less influence on salivary gland function and therefore less likely to lead to dry mouth as a complication.

Borrie (1998) has also noted that for patients with poor detrusor contracture, **Bethanechol** may improve detrusor contractility (Sonda et al. 1979). It serves as an adjunct to intermittent catherization. Bethanechol is discontinued if residual urines do not decrease; there is excessive sweating, asthmatic attacks, congestive heart failure and abdominal cramps.

There are few trials that have evaluated urinary incontinence post stroke. Brittain et al. (1999) have highlighted the importance of distinguishing between urge incontinence and urinary retention, since the management of each is different.

**Table 17.5 Treatment of Urinary Incontinence Post Stroke**

<table>
<thead>
<tr>
<th>Author, Year Country PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wikander et al. (1998) Sweden 4 (RCT)</td>
<td>34 patients randomized to receive either rehabilitation based on Functional Independence Measure (FIM) or conventional rehabilitation based on Bobath technique to regain continence.</td>
<td>Significantly greater proportion of FIM group regained continence than in the Bobath group. Significantly greater improvement in Katz ADL in the FIM group and on Psychological Well-being Index. FIM group showed significantly greater improvement in transferring form wheelchair to toilet, bed to wheelchair and in managing wheelchair compared to Bobath group.</td>
</tr>
<tr>
<td>McDowell et al. (1999) USA 5 (RCT)</td>
<td>105 patients were randomly assigned to biofeedback-assisted pelvic floor training. The treatment group (24.5% stroke patients) received behavioral therapies over an 8-week period with weekly in-home visits from a nurse practitioner. The control group (28.8% stroke patients) underwent 8-weeks of observation and then crossed over to complete the treatment protocol. Outcome Measures included the OARS Physical and Instrumental Activities of Daily Living, Folstein Mini Mental State Examination, Clock Drawing Test, Performance-Based Toileting Assessment, bladder diaries and physical examination.</td>
<td>There was a significant reduction in urinary accidents for the treatment group 75% compared to the control group 6.4% (p&lt;0.001). After the control subjects crossed over to complete the treatment protocol the 85 total patients who completed treatment attained a 73.9% reduction in urinary incontinence. All accidents were reduced by 73.9% for patients who completed the treatment.</td>
</tr>
<tr>
<td>Engberg et al. (2002) USA 6 (RCT)</td>
<td>19 older patients were randomized to a prompted voiding group (30% stroke patients) or a delayed attention control group (56% stroke patients) who participated in an 8-weeks observational period and then crossed over complete to the treatment protocol. Outcome Measures included the OARS Physical and Instrumental Activities of Daily Living scales, Folstein Mini Mental State Examination, Clock Drawing Test, Performance-Based Toileting Assessment, bladder diaries and physical examination.</td>
<td>The treatment group significantly reduced their total incontinent episodes by 55% compared with a 27% reduction for the control group. (p=0.04). After the control subjects crossed over to complete the treatment protocol there was a 22% reduction in daytime incontinent episodes for all subjects completing the treatment (p=0.04).</td>
</tr>
</tbody>
</table>
Tibaek et al. (2005; 2004) Denmark  7 (RCT)  
26 women with urinary incontinence (UI), at a median of 12 months post stroke were randomized to a treatment or a control group in a single blinded study. The intervention included 12 weeks of standardized pelvic floor muscle training. Patients in the control group received standard rehabilitation only. The outcome measures were the Short Form 36 (SF-36) Health Survey Questionnaire and The Incontinence Impact Questionnaire (IIQ). A subsequent publication in 2005 reports on voiding frequency, the number of incontinent episodes and the number of incontinence pads used in a 24 hour period, assessed by 2 and 3 day voiding diary and vaginal palpation.  

Tibaek et al. (2005) Denmark 7 (RCT)  
Six-month follow-up of 24 from 2004 study, assessing indicators of quality of life.  

Tibaek et al. (2007) Denmark 7 (RCT)  
Six-month follow-up of 24 from 2004 study, assessing indicators of quality of life.  

Yun et al. (2007) South Korea 6 (RCT)  
39 stroke patients with urinary symptoms were randomized to receive moxibustion therapy (MO group) (n=20) or to control group (n=19) which did not receive MO for 10 days. The effectiveness of urinary symptoms and activities of daily living were measured by International Prostate Symptom Score (IPSS) and Barthel Index (BI), respectively before treatment, and 10 days after therapy. At the end of treatment subjects in the MO group had significantly higher IPSS scores (5.45 vs. 2.16, p<0.001). There was a significant treatment effect for subjects with mild and moderate symptoms, but not for those with severe. There were no differences between the groups in BI scores (70 vs. 68, p=ns)  

Gross et al. (2007) USA 6 (RCT)  
The purpose of the study was to compare the effect of urinary catheter removal at 7:00 a.m. with removal at 10:00 p.m. on: (a) the length of time to first void after catheter removal, (b) the amount of the first void, (c) post-void residual urine, and (d) the number of subjects requiring re-catheterization. 45 subjects were enrolled: 26 in Group A (10:00 p.m. removal) and 19 in Group B (7:00 a.m. removal). No significant differences were identified between the two groups with regard to time to void, volume of first void, post-void residual urine, or the number of subjects requiring recatheterization.  

Moon et al. (2012) South Korea 4 (RCT)  
The purpose of the study was to investigate the effects of bladder-reconditioning by IUC clamping before IUC removal. Sixty stroke patients were randomized to 0-, 1-, and 3-day IUC clamping groups. Patients in the 1-, and 3-day clamping groups were clamped 4hrs followed by 5min of urinary drainage for 24- and 72-hrs, respectively. There were no significant differences for time to first void (FV), FV-vol, residual urine volume after FV, voiding method, mean voided volume, and residual urine volume among the three groups.
Table 17.6 Summary of RCTs Evaluating Treatments in the Management of Urinary Incontinence Post Stroke

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>PEDro Score</th>
<th>N</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiabek et al. 2004, Tiabek et al. 2005, Tiabek et al. 2007</td>
<td>7</td>
<td>26</td>
<td>Pelvic floor exercises</td>
<td>24 hr pad test (-) Strength, endurance, function of pelvic floor muscle (-) SF-36 (-) IIQ (-)</td>
</tr>
<tr>
<td>Gross et al. 2007</td>
<td>6</td>
<td>45</td>
<td>Timing of catheter removal</td>
<td>Time to void (-) Volume on first void (-) Post-void residual (-)</td>
</tr>
<tr>
<td>Yun et al. 2007</td>
<td>6</td>
<td>39</td>
<td>Moxibustion</td>
<td>IPSS (+)</td>
</tr>
<tr>
<td>Engberg et al. 2002</td>
<td>5</td>
<td>19</td>
<td>Prompted voiding</td>
<td>Incontinent episodes (+)</td>
</tr>
<tr>
<td>McDowell et al. 1999</td>
<td>5</td>
<td>105</td>
<td>biofeedback-assisted pelvic floor training</td>
<td>Urinary accidents (+)</td>
</tr>
<tr>
<td>Wikander et al. 1998</td>
<td>4</td>
<td>34</td>
<td>FIM-based rehabilitation program</td>
<td>Incontinence after treatment (+)</td>
</tr>
<tr>
<td>Moon et al. 2012</td>
<td>4</td>
<td>60</td>
<td>Bladder reconidition through indwelling urethral Catheter (IUC) clamping</td>
<td>Time to first void, volume on first void, voiding method, residual urine volume following first void (-)</td>
</tr>
</tbody>
</table>

A wide variety of treatments is available in the management of incontinence following stroke. However, the pre-stroke continence status, small sample sizes and heterogeneity of treatments and outcomes assessed limit the generalizability of the findings. A single positive RCT was found for each of 4 differing treatments: Moxibustion, a program of prompted voiding, biofeedback assisted pelvic floor training and a FIM-focused rehabilitation unit.

**Conclusions Regarding the Treatment of Urinary Incontinence**

**There is moderate (Level 1b) evidence that prompted voiding significantly reduced the number of total incontinent episodes.**

**There is moderate (Level 1b) evidence that biofeedback-assisted pelvic training and behavioral therapy with weekly in-home visits from a nurse practitioner significantly reduces urinary accidents and incontinence.**

**There is moderate (Level 1b) evidence that a functionally oriented rehabilitation approach results in significantly less incontinence than a Bobath conventional approach.**

**There is moderate (Level 1b) evidence that moxibustion can improve urinary tract symptoms.**

*Prompted voiding and biofeedback-assisted pelvic training plus behavioral therapy and weekly in-home visits reduce incontinent episodes. Treatment with a functionally oriented rehabilitation approach vs. a Bobath approach for urinary incontinence post stroke has not been well studied.*
17.2.4 Urinary Bladder Catheterization Post Stroke

Approximately, 40% of patients regain continence during the first two weeks (Brocklehurst et al. 1985). The use of a catheter will inhibit this process. Catheterization should be reserved for exceptional circumstances (Nazarko 2003). Highlighted circumstances include, urinary retention that can’t be otherwise treated, severely impaired patients with evident skin breakdown whom frequent bed and/or clothing changes are difficult or painful, and patients where incontinence interferes with the monitoring of fluid and electrolyte balance (Gresham et al. 1995). In a recent study, using data from the Taiwan Stroke Registry (TSR), investigators looked at the rates of indwelling urinary catheterization (IUC) after acute stroke (Wu et al. 2013). Approximately, 25% of patients received indwelling catheters following admission, with patients with an intracerebral hemorrhage more likely to have an IUC during acute hospitalization compared to patients with an ischemic stroke (60% vs. 16%, respectively) (Wu et al. 2013).

Previous research shows that the chronic use of indwelling catheters increases the risk of bacteria and UTI (Bjork et al. 1984; Sabanathan et al. 1985; Warren et al. 1982). Furthermore, a substantial amount (“three quarters) of patients who are catheterized for ≥ three months, are found to develop inflammatory bladder wall changes. In a descriptive study that looked to identify key factors influencing doctors’, nurses’, and physiotherapists, decision to have an indwelling catheter inserted in acute stroke patients, clinical indicators (skin, integrity, urinary retention, etc.) was identified as a main reasons for catheterization; however, overall there was a lack of standardized consensus regarding the decision process (Cowey et al. 2012). Given the negative effects that have been found for stroke patients who experience UTIs (please see section 17.2.2 labelled Urinary Tract Infections), a more standardized decision approach concerning catheterization and, thus, a reduced risk for patients acquiring an infection is warranted. Although bacteremia can be identified by urine culture, UTI treatment with antibiotics should be reserved for those patients with symptomatic UTIs.

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 stroke survivor 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. Note, the literature upon which this recommendation was based was not specific to stroke patients.

**Conclusions Regarding the Use of Indwelling Urinary Catheters**

*The use of indwelling catheters in stroke patients has not been well studied. There is consensus (Level 3) opinion that indwelling catheters should be limited to those patients with intractable urinary retention, skin breakdown, continuous wetness and the need for urinary monitoring.*

**Indwelling urinary catheters should only be used for cases of intractable urinary retention, continuous wetness or the need for monitoring.**

17.3 Fecal Incontinence/Constipation Following Stroke

Both constipation and fecal incontinence have been reported following stroke. The reported percentage of patients who experienced some form of fecal incontinence ranged from 7% to 56% (Table 17.6), although it usually resolved within two weeks of stroke. The criteria used to define constipation among...
studies may have contributed to a portion of the variability in the reported incidence. Kovindha et al. (2009) reported that double incontinence (bowel/bladder) was 33% at admission to a rehabilitation unit and 15.1% at discharge. Brittain et al. (2006) reported that major fecal incontinence was 4.5x more prevalent among stroke survivors compared with non-stroke controls.

A variety of risk factors for fecal incontinence have been identified, including total anterior infarction (Barrett 2002). Harari et al. (2003) identified problems with toilet access and constipating drugs as modifiable risk factors post stroke; however, the most powerful predictor of fecal incontinence in the first few days following stroke appears to be the initial level of consciousness.

Constipation following stroke has not been well studied. Although a high prevalence of constipation has been reported, there does not appear to be a directly causal mechanism between stroke per se and constipation. Poor fluid intake, the use of constipation-inducing medications, poor dietary fiber intake and decreased mobility and increased dependence may all be contributory. As such, constipation is viewed as an avoidable complication of stroke, which can be treated in mild cases using stool softeners and pro-kinetic agents. 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 152 rehabilitating stroke patients.

### Table 17.7 The Prevalence/Incidence of Fecal Incontinence Following Stroke

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>N</th>
<th>Prevalence (P)/Incidence (I) and Timing of Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brocklehurst et al. (1985)</td>
<td>135</td>
<td>23% at 2 weeks; 3% at 6 months; 8% at 1 year</td>
</tr>
<tr>
<td>Wade et al. (1985)</td>
<td>532</td>
<td>31% at admission; 7% at 6 mos. (P)</td>
</tr>
<tr>
<td>Fullerton et al. (1988)</td>
<td>205</td>
<td>21% at admission (P)</td>
</tr>
<tr>
<td>Ween et al. (1996)</td>
<td>432</td>
<td>31% at 2 weeks</td>
</tr>
<tr>
<td>Nakayama et al. 1997(1997)</td>
<td>935</td>
<td>40% at admission; 18% at discharge; 9% at 6 mos. (P)</td>
</tr>
<tr>
<td>Pandya et al. (2002)</td>
<td>204</td>
<td>17% at admission; 26% at day 7 (P)</td>
</tr>
<tr>
<td>Baztan et al. (2003)</td>
<td>166</td>
<td>56% at admission; 21% at discharge; 22% at 6 mos. (I)</td>
</tr>
<tr>
<td>Harari et al. (2003)</td>
<td>1468</td>
<td>30% at 7-10 days; 11% at 3 mos.; 11% at 1 year; 15% at 3 years. (I)</td>
</tr>
<tr>
<td>Brittain et al. (2006)</td>
<td>1,483</td>
<td>5% major symptoms (community-dwelling)</td>
</tr>
<tr>
<td>Kovindha et al. (2009)</td>
<td>185</td>
<td>7.6% at admission, 4.9% at discharge</td>
</tr>
<tr>
<td>Su et al. (2009)</td>
<td>160</td>
<td>55.2% within 4 weeks of stroke onset</td>
</tr>
</tbody>
</table>

### 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 the 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 two RCTs have evaluated treatment strategies for constipation/fecal incontinence (Table 17.8).
Table 17.8 Treatment of Fecal Incontinence Post Stroke

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venn et al.</td>
<td>USA</td>
<td>3 (RCT)</td>
<td>58 subjects on a stroke rehabilitation unit were randomly assigned to one of four treatments: i) morning bowel training with mandatory suppository, ii) morning bowel training with optional suppository, iii) evening bowel training with mandatory suppository and iv) evening bowel training with optional suppository.</td>
<td>Subjects assigned to the morning groups were more likely to establish effect bowel movement patterns. There were no differences found between the groups, which required mandatory or optional suppository use.</td>
</tr>
<tr>
<td>Harari et al.</td>
<td>UK</td>
<td>6 (RCT)</td>
<td>146 mainly community-dwelling stroke patients (n=122) with constipation or fecal incontinence were identified and randomized to receive intervention or routine care (73 per group). The intervention consisted of a 1 time nursing assessment (history and rectal examination), followed by patient/carer education with booklet and provision of diagnostic summary and treatment recommendations (after consultation with geriatrician) to patient’s general practitioner (GP)+/-ward physician.</td>
<td>Percentage of bowel movements (BMhs) per week graded as &quot;normal&quot; by participants in a prospective 1-week stool diary was significantly higher in intervention versus control patients at 6 months (72% vs. 55%), as was mean number of BMs per week (5.2 vs. 3.6). There was no significant reduction in fecal incontinence, although numbers were small. At 12 months, intervention patients were more likely to be modifying their diets and fluid intake to control their bowels and to have visited their GP for their bowel problem. GP prescribing of laxatives and suppositories was significantly influenced at 12 months.</td>
</tr>
</tbody>
</table>

Conclusions Regarding the Treatment of Fecal Incontinence/Constipation

There is moderate (Level 1b) evidence that a nursing evaluation/intervention program can be effective in reducing constipation long-term following stroke.

There is moderate (Level 1b) evidence that a morning bowel routine is more effective than an evening bowel routine.

17.4 Venous Thromboembolism Post Stroke

17.4.1 Incidence of Venous Thromboembolism Post Stroke

Deep venous thrombosis (DVT) and subsequent pulmonary embolism (PE) remain a significant cause of morbidity and mortality in stroke patients undergoing rehabilitation (Desmukh et al. 1991). Actual incidence figures for DVT in stroke patients vary considerably; between 22% and 73% (Izzo & Aquino 1986; Landi et al. 1992; Miyamoto & Miller 1980) (Table 17.2). In the absence of prophylaxis, over 60% of dense hemiplegics develop DVTs, 9-15% have pulmonary emboli, with a 1-2% mortality rate (Sioson et al. 1988). Indeed, pulmonary embolism has been reported to be the fourth most common cause of death in the 30 days after stroke, while the risk of thromboembolism still persists thereafter (Bounds et al. 1981). High-risk patients have been identified as having lower limb plegia, reduced consciousness, obesity and having a previous DVT (Imberti & Prisco 2005). The prevalence of DVT among patients admitted for rehabilitation is lower (12-40%) and dependent upon the provision of anticoagulants, mobility status and method of detection used (Wilson & Murray 2005).
Clinical findings of DVT and PE are present in less than half of patients (Brandstater et al. 1992). Peak onset for the development of DVT is between the second and seventh day of stroke onset (Brandstater et al. 1992). The incidence of DVT diagnosed during rehabilitation is between 5% and 11% (Harvey et al. 2004). The incidence of PE after stroke also varies considerably with estimates ranging from 0.8% at 2 weeks (Group 1997) to 39% at 10 days following hemorrhagic stroke (Dickmann et al. 1988). Fatal PE usually results from proximal DVT. Kelly et al. (2001) suggest that since one third of DVTs are proximal and most are silent, the mortality associated with untreated proximal subclinical DVT after stroke is 15%.

Venous thromboembolism usually begins with a calf DVT (Cogo et al. 1993; Nicolaides et al. 1971; Philbrick & Becker 1988). Twenty percent of DVTs do extend into the proximal veins (Brandstater et al. 1992; Kakkar et al. 1969; Lagerstedt et al. 1985). When DVTs causes symptoms, over 80% of those involve the popliteal or more proximal veins (Kearon et al. 1998). Non-extending distal (calf) DVTs rarely cause PEs and as such are rarely worrisome (Kakkar et al. 1969). Proximal (knee or above) DVTs often do and are the source of concern (Kakkar et al. 1969). Pulmonary emboli are not uncommon post-stroke. Most are asymptomatic or unrecognized. Symptomatic PEs can be and fatal.

Brandstater et al. (1992) reviewed 12 studies, which examined either unselected stroke patients, stroke patients excluding hemorrhagic strokes, or hemorrhagic strokes only. Incidence of DVT ranged from 23% - 75% with most studies showing an incidence of DVT around 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).

Brandstater et al. (1992) citing several studies noted that DVT and PE risk continues beyond two weeks, into the phase of active rehabilitation. Two studies in which 118 patients were screened reported 31% of patients admitted to rehabilitation units had a DVT, detected by impedance plethysmography (Izzo & Aquino 1986; Sioson et al. 1988). The mean time between stroke onset and impedance plethysmography screening was about 45 days. Miyamoto and Miller (1980) screened stroke patients with I 125 fibrinogen an average of 9 days following admission to rehabilitation and found a 29% prevalence of DVT. Cope et al. (1973) reported a DVT prevalence of 31%, detected by venography in patients admitted to a rehabilitation centre.

Brandstater et al. (1992) also reported that clinical symptoms of a DVT (pain, swelling, erythema) were often absent, even when diagnostic tests were positive. In their summation of six studies, these authors noted that symptoms occurred in only 52 of 138 cases with positive I 125 fibrinogen scans (Bornstein & Norris 1988; Denham et al. 1973; Elias et al. 1990; Gibberd et al. 1976; Sioson et al. 1988; Warlow et al. 1976). Other studies cited in this review demonstrated that clinically silent DVTs are often diagnosed using diagnostic tests in the subacute phase. On admission to a rehab 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).

Kelly et al. (2004) identified advanced age and a Barthel Index score of 9 or less as the two major risk factors for the development of DVT two days following stroke using a multivariable regression model including 102 acute ischemic stroke patients.

Gregory and Kuhlemeier (2003) investigated the prevalence of DVTs in both hemorrhagic and thromboembolic stroke patients hospitalized acutely. They found that the presence of hemorrhagic stroke was an independent risk factor for DVT (p<0.0007). An additional risk factor for DVT included
increased length of hospital stay (p<0.00001). Also, Skaf et al. (2005) observed a surprisingly increased rate of PE, DVT and VTE in hemorrhagic stroke patients in comparison to ischemic stroke patients. Although, they noted that the ischemic stroke patients use antithrombotic prophylaxis more frequently which could account for the rate difference in hemorrhagic patients.

A recent review of the Registry of the Canadian Stroke Network in 2013 by the Stroke Outcomes Research Canada Working Group reports a similar incidence of PE (Pongmoragot et al. 2013). The registry contains information on 11,287 patients with acute ischemic stroke. PE was identified in 0.78% of acute ischemic stroke patients and was associated with 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) as well as disability at discharge (85.4% vs. 63.6%; P<0.001) (Pongmoragot et al. 2013).

### Table 17.9 Incidence of DVT Post Stroke

<table>
<thead>
<tr>
<th>Author, Year Country</th>
<th>PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warlow et al. (1976) UK</td>
<td>No Score</td>
<td>76 patients with hemiplegia admitted within 48 hours of acute stroke. DVT was diagnosed using radiolabeled fibrinogen, conducted daily for 10 days. No patients were treated with prophylactic heparin</td>
<td>40 (53%) developed a DVT. Of these, clinical signs occurred in 24 of the 40 paralysed limbs. Only the presence of varicose veins had a statistically significant association with the development of DVT.</td>
</tr>
<tr>
<td>Miyamoto &amp; Miller (1980) USA</td>
<td>No Score</td>
<td>141 stroke patients undergoing intensive rehabilitation were evaluated for the presence of DVT 10 days to 2 weeks following stroke.</td>
<td>29% prevalence of DVT identified by I-125-fibrinogen uptake leg scans.</td>
</tr>
<tr>
<td>Sioson et al. (1988) USA</td>
<td>No Score</td>
<td>Impedance plethysmography was performed on 105 consecutive stroke patients admitted to a rehabilitation hospital.</td>
<td>32/98 patients had evidence of new DVT. Weakness, male gender, interval between stroke and screening, edema and leg hyperpigmentation were associated with the development of DVT.</td>
</tr>
<tr>
<td>Landi et al. (1992) Italy</td>
<td>No Score</td>
<td>70 consecutive acute stroke patients were evaluated to identify the presence of DVT during the first 10 days of hospitalization. Serial venous dopplers and iodine 125-labelled fibrinogen uptake tests were used.</td>
<td>20 patients (28.6%) developed a DVT following entry into the study. 15 of these patients died during hospitalization. At autopsy, a pulmonary embolus was discovered in 8 of these patients</td>
</tr>
<tr>
<td>Oczkowski et al. (1992) Canada</td>
<td>No Score</td>
<td>102 consecutive patients undergoing rehabilitation for stroke received Impedance plethysmography (IPG) as routine screening and in patients with symptoms of deep venous thrombosis (DVT).</td>
<td>Venous thromboembolism was documented in 11 patients (11%) an average of 60 days after stroke onset. 2 patients (2%) died from PE. DVT was found on routine IPG screening in 6 patients and verified by IPG in two clinically symptomatic patients. The odds of developing venous thromboembolism were 17.6 higher in patients who were bedridden or wheelchair-bound at the time of admission.</td>
</tr>
<tr>
<td>Kelly et al. (2004) UK</td>
<td>No Score</td>
<td>The prevalence and clinical risk factors for DVT was assessed using magnetic resonance direct thrombus imaging, among 102 unselected patients with acute ischemic stroke receiving standard prophylaxis (aspirin and graded compression stockings (GCS)). Mean follow-up period was 21 days.</td>
<td>The prevalence of all DVT, proximal deep vein thrombosis (PDVT), and pulmonary embolism (PE) were 40%, 18%, and 12%. Among patients with a Barthel Index score of ≤ 9 2 days after stroke, the prevalence increased (63%, 30%, and 20%). Clinical DVT and PE occurred in 3% and 5% overall; half these events were overlooked by the attending team. The true incidence of</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Country</td>
<td>Score</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>Skaf et al. (2005)</td>
<td>USA</td>
<td>No Score</td>
<td>The rates of pulmonary embolism (PE), deep venous thrombosis (DVT), and their combination, venous thromboembolism (VTE), in hospitalized patients with stroke from 1979 to 2003 were determined from the National Hospital Discharge Survey.</td>
</tr>
<tr>
<td>Zorowitz et al. (2005)</td>
<td>USA</td>
<td>No Score</td>
<td>The Post-Stroke Rehabilitation Outcomes Project database of 1161 patients was used to describe the incidence and temporal sequence of DVT along with trends in treatment and prevention of DVT.</td>
</tr>
<tr>
<td>De Silva et al. (2006)</td>
<td>Singapore</td>
<td>No Score</td>
<td>111 acute ischemic Asian stroke patients received hrombo ultrasound scans of the lower limbs performed at days 7-10 and 25-30 after stroke onset. Assessments were done at 6-months to evaluated functional status using the modified Rankin Scale.</td>
</tr>
<tr>
<td>Hara (2008)</td>
<td>Japan</td>
<td>No Score</td>
<td>272 consecutively admitted rehabilitation inpatients who had experienced an ischemic stroke were prospectively evaluated for the development of DVT. Suspected cases of DVT were identified by imbalance in calf circumference + clinical symptoms. Diagnosis was confirmed using D-dimer assay and venous duplex ultrasonography.</td>
</tr>
<tr>
<td>Chua et al. (2008)</td>
<td>Singapore</td>
<td>No Score</td>
<td>419 consecutively admitted rehabilitation inpatients with either ischemic or hemorrhagic stroke were prospectively evaluated for the development of DVT. The screening protocol included a quantitative D-dimer assay within 24 to 48 hours of rehabilitation admission, and hemiplegic/weaker lower-extremity venous duplex ultrasonography was performed if D-dimer assay level was elevated at 0.34 microg/mL or higher.</td>
</tr>
<tr>
<td>Dennis et al. (2011)</td>
<td>UK</td>
<td>No Score</td>
<td>5,632 immobile patients were recruited for the CLOTS I &amp; II trials. The incidence of DVT was compiled from this cohort, as evaluated using compression duplex ultrasound.</td>
</tr>
</tbody>
</table>
Conclusions Regarding the Incidence of Deep Venous Thromboembolism

There is wide variability in the reported incidence of DVT following stroke. The incidence of DVTs which are both clinically apparent and silent may be as high as 45% acutely post stroke. This rate may fall to 10% or lower in patients in the sub-acute phase of stroke receiving rehabilitation.

The incidence of DVT is less than 10% in the rehabilitation phase.

17.4.2 Diagnosis of Venous Thromboembolism Post Stroke

The signs and symptoms of PE are nonspecific and can include: sudden chest pain, shortness of breath, difficulty breathing, or rapid breathing, coughing up blood, loss of consciousness (fainting), which often leads to difficulties with diagnosis. Due to physical and cognitive impairment patients may be unable to verbalize complaints. Pneumonia, relatively common following stroke, is often mistaken for a PE (Kelly et al. 2001). Several methods and techniques are currently used for diagnosis the most popular is the Wells Score or criteria:

<table>
<thead>
<tr>
<th>Condition/Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (or treatment in the last 6 months or palliative)</td>
<td>+1</td>
</tr>
<tr>
<td>Calf swelling ≥ 3cm compared to asymptomatic side</td>
<td>+1</td>
</tr>
<tr>
<td>Swollen unilateral superficial veins on symptomatic side</td>
<td>+1</td>
</tr>
<tr>
<td>Unilateral pitting edema</td>
<td>+1</td>
</tr>
<tr>
<td>Previous DVT</td>
<td>+1</td>
</tr>
<tr>
<td>Selling of entire leg</td>
<td>+1</td>
</tr>
<tr>
<td>Localized tenderness along the deep venous system</td>
<td>+1</td>
</tr>
<tr>
<td>Paralysis, paresis or recent cast immobilization of LE</td>
<td>+1</td>
</tr>
<tr>
<td>Recently bedridden ≥ 3 days, or major surgery requiring regional or general anesthetic in the past 12 weeks</td>
<td>+1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely</td>
<td>-2</td>
</tr>
<tr>
<td>Score: Low risk &lt; 1 (5%), Moderate risk 1-2 (17%), High risk ≥ 2 (53%)</td>
<td></td>
</tr>
</tbody>
</table>

Venous Ultrasound

Venous ultrasound is often used to diagnose a DVT. The sensitivity of the test is 95% in all patients with symptomatic proximal DVTs. The sensitivity falls to 73% for distal DVTs. However, distal DVTs are generally not dangerous until they extend proximally at which they are at a much higher risk of going up to become a pulmonary embolus. Since the majority of DVTs that do so extend within the first week and serial testing may be used if the test is negative but the patient is still symptomatic – the test is likely to become positive if the clot extends. Recent studies have begun looking at ultrasounds utility in predicting DVT risk (Ogata et al. 2013). While admission venous diameter in the posttibial veins (PTV) and peroneal veins (PV) did not correlate with DVT risk venous diameter at 2 weeks, they were significantly larger in those who developed DVT’s compared with those without DVT (PTV p=.033, PV p=.015).
Venography
Venography is considered a definitive test for DVT and is an invasive study whereby contrast dye is injected into the leg veins. Diagnosis of DVT is made if an intraluminal-filling defect is noted.

D-Dimer Assay
D-dimer assay tests are a rapid, non-invasive and inexpensive test (Gill & Nahum 2000). Fibrin is the main component of thrombus formation – fibrin degradation products include d-dimers (Gill & Nahum 2000). A positive d-dimer test is highly sensitive but lacks specificity since d-dimers are found in other disease states, including cancer, congestive heart failure and inflammatory conditions (Raimondi et al. 1993). D-dimer assays have a high negative predictive value, which means when it is negative it is unlikely that the patient has a DVT. However, it has poor positive predictive value so that when it is positive it could be something else and you don’t know if in fact a DVT accounts for the clinical picture. To illustrate, 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 rehabilitating patients admitted with a diagnosis of stroke, spinal cord injury, hip arthroplasty or traumatic brain injury. The specificity and positive predictive value were low, at 55.3% and 48.7%. Generally, if the D-dimer level is less than 0.5μg/ml it is negative. Linkins et al., (2013) studies the use of “Selective D-dimer” testing on suspected first DVT post stroke and found that with a low clinical suspicion and a cutoff of 1.0μg/ml (less than 1.0μg/ml = negative test) the specificity increased to 95% while the sensitivity remained at 98%.

Diagnosis of DVT
A positive diagnosis of a DVT can only be made if the venogram is positive or there is a positive venous ultrasound at two or more sites of the proximal veins. A negative diagnosis for DVT can be made if there is a negative venogram, a negative d-dimer test or a normal venous ultrasound assuming the venous ultrasound is accompanied by one of the following findings: 1) low clinical suspicion for DVT, or 2) normal d-dimer test, or 3) normal serial testing with testing conducted one week later.

Clinical Presentation of Pulmonary Embolus
The clinical diagnosis of pulmonary emboli is unreliable, being both insensitive and nonspecific. Many cases are clinically silent with only 30% having the clinical features of a DVT and only 70% demonstrating a DVT on venography. Patients with a massive pulmonary embolus who suffer compromise of more than 60% of the pulmonary circulation are critically ill. Right heart failure may progress to cardiovascular collapse with hypertension, coma and death. A submassive pulmonary embolus presents with tachycardia, tachypnea and signs of pulmonary infarction with consolidation, rales, hemoptysis, pleuritic chest pain, pleural friction rub, pleural effusion and fever. In most cases there are usually only a few clinical findings and the presentation may be nonspecific with the major clinical complaints malaise and a fever.

Ventilation/Perfusion Scanning
Nuclear ventilation/perfusion scans are often used to diagnose a PE. A normal perfusion scan excludes a PE but is found in the minority of patients with a PE. Perfusion defects are non-specific; about a third of those with defects actually have a PE. The probability that a perfusion defect is a PE increases with the size, shape and number of defects as well as the presence of a normal ventilation scan. Mismatched perfusion defects (normal ventilation scan), which are segmental in size or larger are “high probability” defects and are associated with approximately an 80% prevalence of PE. Three or more mismatched defects are associated with a prevalence of approximately 90%. If a patient has a positive V/Q scan and high clinical suspicion of a PE then they should be treated.
Table 17.10 Probability of pulmonary embolism based on ventilation-perfusion scan results and clinical suspicion in PIOPED study

<table>
<thead>
<tr>
<th>Ventilation-perfusion scan results</th>
<th>Clinical suspicion of pulmonary embolism*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>High probability</td>
<td>56%</td>
</tr>
<tr>
<td>Intermediate probability</td>
<td>16%</td>
</tr>
<tr>
<td>Low probability</td>
<td>4%</td>
</tr>
<tr>
<td>Normal/near-normal probability</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Percentage of patients with pulmonary embolism
Adapted from the PIOPED Investigators (Gill and Nahum 2000, PIOPED Investigators 1990).

PIOPED demonstrated that a low-probability or normal ventilation-perfusion scan with a low clinical suspicion of pulmonary embolism essentially excludes the diagnosis of pulmonary embolism (negative predictive values 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).

Pulmonary Angiography
Pulmonary angiography is the definitive diagnosis for pulmonary embolism (Gill & Nahum 2000). It involves percutaneous catheterization and injection of contrast dye into a pulmonary artery branch (Gill & Nahum 2000). It is used when the V/Q scan is nondiagnostic but the clinical suspicion remains high. It is an expensive test and is associated with some significant risk of complications. Relative contraindications include significant bleeding risk, allergy to contrast medium, and renal insufficiency (Gill & Nahum 2000). It is associated with a mortality rate of up to 0.5% (Newman 1989; Stein et al. 1992). Pulmonary angiography is most commonly used when ventilation-perfusion scanning is nondiagnostic but clinical suspicion remains high (Tapson et al. 1999). A negative pulmonary angiogram excludes clinically relevant pulmonary embolism (Gill & Nahum 2000; Tapson et al. 1999).

Spiral CT Scan
A spiral CT scan is a quick CT scan which can scan the entire thorax in one breath-hold. It has a sensitivity ranging from 64-93% with a specificity of 89-100% - it is most accurate when the embolism is large and less accurate when the clot is small. It actually visualizes the clot and has the added benefit of diagnosing other disease states in the differential diagnosis. It is also a less expensive test. The majority of ventilation perfusion scans have nondiagnostic results, requiring further testing (PIOPED Investigators 1990).

17.4.3 Prophylaxis of Venous Thromboembolism Post Stroke

Anticoagulants can prevent thrombi from forming in the deep veins of the leg, which can then break off and travel to the lungs, resulting in a pulmonary embolism (PE); the most clinically important consequence of DVT. However anticoagulants can lead to serious complications such as intracerebral hemorrhaging. The risks and benefits were recently debated by Adams (2004), a proponent of their use, as standard therapy and Dennis (2004) who argues that the routine use of oral anticoagulants should be reserved for special cases where patients are believed to be at high risk. Guidelines vary. For example, Guidelines for the Early Management of Patients with Ischemic Stroke, a scientific statement from the Stroke Council of the American Stroke Association (Adams et al. 2003) states “the subcutaneous administration of anticoagulants or the use of intermittent compression stockings or aspirin for patients who cannot receive anticoagulants is strongly recommended to prevent DVT among immobilized
patients”. However, in the UK, the routine use of heparin is no longer recommended for prevention of DVT following ischemic stroke, where standard therapy includes aspirin and compression stockings. The authors of the CLOTs trials attempted to develop a prediction model to identify immobile patients at higher risk of the development of DVT to aid in treatment decisions (Dennis et al. 2011). While a few factors including dependency before stroke, a history of DVT/PE, an inability to lift arms off the bed and diabetes were all identified as independent predictors, the resulting model did not discriminate well between patients who did and did not develop DVTs.

The Canadian Best Practice Recommendations for Stroke Care state that patients at high risk of venous thromboembolism should be started on venous thrombo-embolism prophylaxis immediately [Evidence Level A] (Lindsay et al. 2010).

a. Low molecular weight heparin should be considered for patients with acute ischemic stroke at high risk of venous thromboembolism; or unfractionated heparin for patients with renal failure [Evidence Level B].

b. The use of anti-embolism stockings alone for post-stroke venous thrombo-embolism prophylaxis is not recommended [Evidence Level A].

Pharmacological Agents for DVT Prophylaxis

Unfractionated Heparin (UFH)

Heparin acts as an anticoagulant by forming a complex with antithrombin, catalysing the inhibition of several activated blood coagulation factors: XIIa, Xla, IXa, Xa and thrombin. Heparin’s onset of action is immediate. It is most often uses in acute conditions, and must be given parenterally. Although low molecular weight heparin 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. Osteoporosis is associated with the prolonged use of high doses of heparin, although its occurrence is infrequent. Thrombocytopenia is an uncommon but serious side-effect of the treatment (Pineo 2004).

<table>
<thead>
<tr>
<th>Low Molecular Weight Heparin (LMWH)</th>
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<tbody>
<tr>
<td><strong>Generic Name</strong></td>
</tr>
<tr>
<td>Dalteparin</td>
</tr>
<tr>
<td>Danaparoid</td>
</tr>
<tr>
<td>Enoxaparin</td>
</tr>
<tr>
<td>Ardeparin</td>
</tr>
<tr>
<td>Parnaparin, Reviparin</td>
</tr>
<tr>
<td>Tinzaparin</td>
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<tr>
<td>Certoparain</td>
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</tbody>
</table>

Low-molecular-weight heparin (LMWH) is derived from standard heparin through either chemical or enzymatic depolymerization. Whereas standard heparin has a molecular weight of 5,000 to 30,000 daltons, LMWH ranges from 1,000 to 10,000 Daltons. LMWH binds less strongly to protein, has enhanced bioavailability, interacts less with platelets and yields a very predictable dose response. The clinical advantages of LMWH include predictability, dose-dependent plasma levels, a long half-life and less bleeding for a given antithrombotic effect. Thrombocytopenia is not associated with short-term use of low-molecular-weight heparin. 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 (aPTT) does not need to be monitored, and the dosage does not need to be adjusted (Rydberg et al. 1999).
Heparin Analogues
Danaparoid sodium (Orgaran) is an alternative anticoagulant for patients who develop heparin-induced thrombocytopenia from heparin therapy. Danaparoid is a low molecular weight heparinoid. Its active components consist of heparin sulfate, dermatan sulfate and chondroitin sulfate. The major difference between danaparoid and other low molecular weight heparins (LMWH) is that danaparoid is devoid of heparin or heparin fragments. However, it exerts effects similarly to other LMWHs. Danaparoid acts by inactivating thrombin.

Warfarin (Coumadin)
Warfarin (Coumadin) is the most widely prescribed oral anticoagulant. As an agonist of vitamin K, warfarin acts by inhibiting the synthesis of clotting factors. Therapeutic doses of warfarin reduce the production of functional vitamin K-dependent clotting factors by approximately 30 to 50 percent. Antagonism of vitamin K reduces the rate at which these factors and proteins are produced (Horton & Bushwick 1999). Clinical evidence indicates that an International Normalized Ratio (INR) of 2.0-3.0 is sufficient for prophylaxis and treatment of venous thromboembolism while minimizing the risk of hemorrhage associated with higher INRs.

The antithrombotic effect of warfarin, or the inability to expand or form clots, is not present until approximately the fifth day of therapy. Therefore, concomitant use of heparin is usually required during the transition in therapy. To ensure continuous anticoagulation, it is advisable to continue full dose heparin therapy and therefore Coumadin needs to be overlapped with heparin for 4 to 5 days, until Coumadin has produced the desired therapeutic response as determined by the PT/INR. When Coumadin has produced the desired PT/INR or prothrombin activity, heparin may be discontinued. A small decrease in the INR will likely occur once unfractionated heparin therapy is discontinued. The presence of a therapeutic INR does not confer protection from clot formation and expansion during the first few days of warfarin therapy because of the delay in the therapeutic inhibition of prothrombin (Horton & Bushwick 1999).

Previous Reviews
Bath et al. (2000) conducted a systematic review evaluating the safety and efficacy of LMWH, including dalteparin, danaparoid, mesoglycan, nadroparin and tinzaparin. The analysis included the results from 11 studies and 3,048 subjects. The treatment contrast assessed was LMWH compared with placebo. While treatment was associated with a significant reduction in the occurrence of DVT (OR: 0.27, 95% CI 0.08 to 0.96) it was accompanied by a significant increase in the risk of extracranial hemorrhage (OR: 2.17, 95% CI 1.10 to 4.28). The authors concluded that LMWH should not be used routinely following ischemic stroke.

An updated Cochrane review authored by Sandercock and Counsell (2008) compared the effectiveness of low molecular weight heparin (LMWH) compared to unfractionated heparin (UFH) following acute ischemic stroke. Nine RCTs including 3,137 patients were included. The authors noted that the assessment of DVT was inadequate in many of the trials, so they performed a modified worst-case scenario analysis. Overall, heparinoid was associated with a significant reduction in the DVT (OR=0.55, 95% CI 0.44-0.70). The number of adverse events, including PE and death were considered too small to provide reliable estimates of risk and benefit, therefore the safety profile of the two agents could not be established. While UFH is in widespread clinical use, there is also an associated, increased (dose-dependent) risk of intra- and extra-cranial hemorrhage. Since LMWH and heparin analogues have more specific sites of action, they may also be associated with lower rates of hemorrhage. It had been noted up to that time that there was an associated dose-dependent risk of intra- and extra-cranial hemorrhage.
with UFH. It was speculated that LMW Heparin with its more specific action would have lower rates of hemorrhagic complications.

Van Dongen et al. (2004) conducted a Cochrane review comparing the effects of fixed-dose, subcutaneous LMWH and adjusted-dose, intravenous or subcutaneous, unfractionated heparin for initial treatment of acute deep venous thrombosis or pulmonary embolism among patients with a range of diseases. Twenty-two studies were included (n = 8867). Thrombotic complications occurred in 3.6% of patients treated with LMWH, compared with 5.4% treated with unfractionated heparin (UFH) (OR= 0.68; 95% CI: 0.55 to 0.84). Major hemorrhages occurred in 1.2% of patients treated with LMWH, compared with 2.0% of patients treated with UFH (OR= 0.57, 95% CI; 0.39 to 0.83, 19 trials). Mortality was higher among patients treated with UFH. In subgroup analyses, there were statistically significant reductions in thrombotic complications and major hemorrhage, favouring LMWH. The authors concluded that LMWH is as good as UFH for the initial treatment of DVT and significantly reduced the occurrence of major hemorrhage, both during initial treatment and overall mortality at follow up.

In a systematic review, Gubitz et al. (2004) examined the effects of all forms of anticoagulation following ischemic stroke. One of the aims of the study was to assess the effectiveness of anticoagulation therapy on the reduction of DVT incidence, identified by I-125 scan, leg ultrasound, plethysmography or x-ray contrast venogram. Anticoagulation therapy included unfractionated heparins, low molecular weight heparins, heperanoids and oral anticoagulants. Although the review included only 3.9% of patients included in the individual RCTs, the reduction in odds of DVT associated with any anticoagulation therapy, compared to a placebo control condition, was dramatic (OR=0.21, 95% CI 0.15-0.29). The authors suggested that the trials, which were considered positive, differed from negative trials in their diagnostic evaluation of DVT, the three negative trials did not use I-125 fibrinogen scanning. One of the negative trials randomized patients within 14 days of the stroke event, while patients were randomized within 7 days in the remaining trials. However, most of the DVTs identified in the review were asymptomatic. The odds of pulmonary embolism (PE) associated with all forms of anticoagulation were also reduced by 79% (OR=0.60, 95% CI 0.44-0.81); the equivalent of 4 PEs avoided per every 1,000 patients treated. However, the risk of major extracranial hemorrhage was increased (9 per 1,000 patients treated). Although anticoagulation reduced the odds of DVT occurrence, there was no associated reduction in death or dependency at the end of follow-up.

Kamphuisen and Agnellu (2007) conducted a review investigating the benefit/risk ratio from pharmacological prophylaxis for venous thromboembolism in acute ischemic stroke patients. Sixteen randomized controlled trials were included (n=23,043). The studies included had small number of events and varied in anticoagulant treatment doses. High-dose unfractioned heparin (UFH) was associated with decreased pulmonary embolism (PE), increased intracranial hemorrhage (ICH) and increased extracranial hemorrhage (ECH) in comparison to control. Low-dose unfractionated heparin reduced the risk of thrombosis, however no effect was seen on PE; there was no significant increase in the risk of ICH and ECH. High-dose low-molecular-weight heparin reduced the incidence of DVT and PE, but increased the risk of ICH or ECH. Low-dose low-molecular-weight heparin decreased DVT and PE, and maintained the risk of ICH or ECH. The authors concluded low-dose LMWH is the most effective treatments when considering the benefit/risk ratio in acute ischemic stroke patients.

Laporte et al. (2011) analyzed patients-level data from 4 RCTs that compared the use of UHF (5000 IU s.q 2-3 times daily) and enoxaparin (4000 IU s.q once daily) in the prevention of DVT. The analysis included the results from two trials restricted to acute stroke patients (Hillbom et al. 2002; Sherman et al. 2007). Compared with UFH, enoxaparin was superior in the prevention of venous thromboembolism (VTE), including both DVT and PE. Enoxaparin use was associated with risk reductions of 37% for total VTE and
62% for symptomatic VTE at day 15. The relative risk associated with the use of enoxaparin among stroke patients was 0.59 (95% CI 0.47-0.74). The incidence of major bleeding episodes was similar between groups. There was a trend towards reduced risk for mortality in patients receiving enoxaparin (RR 0.83, 95% CI 0.64-1.08), compared with UFH.

The use of anticoagulants to reduce the risk of DVT following intracerebral hemorrhage is controversial, due to the increased risk of bleeding. To clarify its safety and efficacy in hemorrhagic stroke, Paciaroni et al. (2011) conducted a meta-analysis including the results from 4 trials (2 RCTs & 2 controlled trials) evaluating the treatment contrasts of LMWH or UFH compared to either a no treatment control or compression stockings. Treatment was initiated within 6 days and continued for up to 14 days. At follow-up (10 days to 3 months) there was a non significant decrease in DVT risk (RR: 0.77; 95% CI: 0.44 to 1.34) and death (RR: 0.76; 95% CI:0.57 to 1.03) favouring the heparin groups. There was a reduction in the risk of PE (RR: 0.37; 95% CI: 0.17 to 0.80) and a non significant risk in hematoma enlargement (RR: 1.42; 95% CI: 0.57 to 3.53). The authors noted that there is no consensus with regard to the use of lose-dose heparin for the prevention of DVT in clinical practice.

<table>
<thead>
<tr>
<th>Author, Year Country</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Unfractionated Heparin or LMWH vs. Placebo or Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCarthy et al. (1977) UK 5 (RCT)</td>
<td>32 stroke patients diagnosed with a stroke in previous 24 hours were randomized to receive either low dose heparin every 8 hours for 14 days or to receive no heparin. All patients received potassium iodide daily for 14 days.</td>
<td>Treatment with heparin was associated with a significant reduction of positive isotope leg scans from 75% to 12.4%.</td>
</tr>
<tr>
<td>McCarthy &amp; Turner (1986) UK 4 (RCT)</td>
<td>305 stroke patients with a diagnosis of stroke in previous 24 hours were randomized to receive either 5000 units of calcium heparin s.c. hourly for 8 hours for 14 days. Control group received no heparin.</td>
<td>Incidence of DVT was significantly lower in the Heparin group than in the control. Reduction in DVT rate from 72.1% in control group to 22.2% in treatment patients was achieved.</td>
</tr>
<tr>
<td>Turpie et al. (1987) Canada 7 (RCT)</td>
<td>75 patients assessed within 7 days post-stroke were randomized to receive either Orgaran (low molecular weight heparin) prophylaxis or placebo for 14 days or until discharge from hospital if earlier than 14 days.</td>
<td>DVT occurred significantly less often in treatment group compared to placebo group (4% vs. 28%).</td>
</tr>
<tr>
<td>Prins et al. (1989) Netherlands 6 (RCT)</td>
<td>60 patients with acute ischemic stroke were randomized to receive either placebo or the LMWH, Fragmin, subcutaneously twice daily for 14 days. A fibrinogen scan was used daily to confirm the development of a DVT.</td>
<td>Both treatment groups were comparable with regard to neurological status and general condition. In the Fragmin group, there were 6 cases of (DVT) compared to 15 in the placebo group at the end of the follow up period (p = 0.05). In the placebo group there were 4 deaths and 2 cases of cerebral bleeding compared to 9 and 4 respectively in the Fragmin treated group. Neither of these results was statistically significant.</td>
</tr>
<tr>
<td>Sandset et al. (1990) Norway 8 (RCT)</td>
<td>103 stroke patients were randomized to receive either low molecular weight heparin once daily or to receive a saline placebo for 14 days or until discharge if earlier.</td>
<td>No significant difference between thrombosis, Motricity Index score and mortality between the two groups.</td>
</tr>
<tr>
<td>Kay et al. (1995) Hong Kong</td>
<td>312 acute stroke patients were randomized to receive either 4100 U Fraxiparine 2 x daily for 10 days (high During the study period there was only one occurrence of DVT (control group). At the end of</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Location</td>
<td>Design</td>
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<td>-------</td>
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</tr>
<tr>
<td>RCT</td>
<td>102</td>
<td>4100 U Fraxiparine once daily (low dose LMWH, n=101) or placebo (n=105)</td>
</tr>
<tr>
<td>TOAST (1998) USA</td>
<td>1281 acute stroke patients from 36 centres were randomized to receive Orgaran (0.6-0.8 anti-Xa U/ml by continuous infusion (n=641) or placebo (n=634) for 7 days.</td>
<td>During the treatment period no patients in the treatment group experienced a DVT while 2 did in the placebo group. At the end of 3 months fewer patients in the treatment group had suffered a DVT (2 vs. 10, p&lt;0.05) There were significantly more occurrences of major bleeding in treatment group (37 vs. 18, p&lt;0.05).</td>
</tr>
<tr>
<td>Orken et al. (2009) Turkey</td>
<td>75 patients with primary intracerebral hemorrhage were randomized to receive subcutaneous LMWH (Enoxaparin sodium 40mg/d) or long compression stockings (CS, which was considered the control condition) after the first 48 hours. All patients had cranial computed tomography (CT) scan at admittance, 24th and 72nd hours, seventh and 21st days, CT pulmonary angiography and bilateral lower extremity venous Doppler at 7th day. Hematoma volumes were calculated on the initial and follow-up CTs.</td>
<td>Following randomization there was no evidence of hematoma enlargement at 72 hours, 7 and 21st days in either groups. There were no other systemic bleeding complications in LMWH group. There was no difference in the incidence of asymptomatic DVT (3 in LMWH and 1 in CS group, p=1.0).</td>
</tr>
<tr>
<td>Low Molecular Weight Heparin vs. Unfractionated Heparin or Other Agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turpie et al. (1992) Canada</td>
<td>A double blind trial of 87 stroke patients assessed within 7 days post-stroke were randomized to receive either low-molecular heparin (Orgaran) or to unfractionated heparin subcutaneously twice daily for 14 days or until discharge if earlier.</td>
<td>Incidence of DVT was significantly lower in Orgaran group compared to heparin 9% vs. 31%</td>
</tr>
<tr>
<td>Dumas et al. (1994) France</td>
<td>A double blind trial of 179 stroke patients screened within 72 hours on onset were randomized to receive either Organon 10172 once daily or heparin sodium twice daily for a minimum of 9 days.</td>
<td>No significant difference in the number of patients developing DVT in each group.</td>
</tr>
<tr>
<td>Hillbom et al. (2002) Finland</td>
<td>Equivalency trial. 212 stroke patients were randomized within 48 hrs of onset of symptoms to receive either enoxaparin (n=106) or unfractionated heparin (UFH) (n=106) for 10 days.</td>
<td>The rate of thromboembolic events (DVT and PE) after 3 mos. were lower in the enoxaparin group compared to UFH (19.7% vs. 34.7%, p=0.044).</td>
</tr>
<tr>
<td>Diener et al. (2006) Germany</td>
<td>Equivalency trial. 272 acute stroke patients received 3000 U of certoparin (LMWH) once daily and 273 patients received 5000 UFH 3 x daily for 12 to 16 days.</td>
<td>During the treatment period 17 patients in the certoparin group experienced DVT compared with 24 in the UFH group (p=0.29). No patient in either group experienced a PE. At the end of 3 months there was a non significant increase in mortality in the certoparin group (14 vs. 8). Bleeding complications were similar between groups.</td>
</tr>
<tr>
<td>Sherman et al. (2007) PREVAIL</td>
<td>1,762 patients with acute ischemic stroke unable to walk were randomized to receive either LMWH 40 mg enoxaparin once daily (n=844) or 5,000 U UFH twice daily (n=878) for 10 days. Open-label study.</td>
<td>The incidence of symptomatic DVT was 1 in the LMWH group and 4 in the UFH group at the end of 14 days (p=0.18). There were fewer incidences of asymptomatic DVT in the LMWH group (66 vs. 114, p&lt;0.0001). The occurrence of any bleeding events was similar between</td>
</tr>
<tr>
<td>Study Reference</td>
<td>Country</td>
<td>Score</td>
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<td>-----------------</td>
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<td>-------</td>
</tr>
<tr>
<td><strong>Mukand &amp; Mukand</strong> (2010) USA</td>
<td>No Score</td>
<td>A review of 54 stroke rehabilitation inpatients who had received either 40 mg enoxaparin or 2.5 mg of Fondaparinux subcutaneously daily until they were mobile (able to walk 150 ft). Patients had been assessed clinically on a daily basis for evidence of DVT and PE and received an ultrasound study if DVT was suspected.</td>
</tr>
<tr>
<td><strong>Heparin vs. Other Treatments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desmukh et al. (1991) USA</td>
<td>1 (RCT)</td>
<td>101 stroke patients randomized to one of three treatment groups or to a control group. In addition to bilateral stockings, patients received one of 3 treatments for DVT prophylaxis (adjusted dose heparin, electrical muscle stimulation or external pneumatic compression) for 28 days or until discharge.</td>
</tr>
<tr>
<td>Pambianco et al. (1995) USA</td>
<td>5 (RCT)</td>
<td>360 stroke patients assessed within 24 hours of stroke onset were randomized to one of three treatment groups or to a control group. Patients received one of 3 treatments for DVT: 1) prophylaxis adjusted dose heparin, 2) electrical muscle stimulation or 3) external pneumatic compression for 28 days or until discharge.</td>
</tr>
<tr>
<td>Bath et al. (2000) (TAIST trial) UK</td>
<td>7 RCT</td>
<td>1486 acute stroke patients were randomized to receive high dose tinzaparin (175 anti-Xa IU/kg daily, n=487), medium dose tinzaparin (100 anti-Xa IU/kg daily, n=508) or 300 mg of aspirin daily (n=491) for up to 10 days in an effort to assess their safety and efficacy in improving functional outcome.</td>
</tr>
<tr>
<td>Berge et al. (2000) (HAEST Group) Norway</td>
<td>9 RCT</td>
<td>449 acute stroke patients were randomized to receive LMWH (100 I/kg 2x/day dalteparin) (n=224) or 160 mg of aspirin every day for 14 days (n=225) for the prevention of recurrent stroke in patients with atrial fibrillation.</td>
</tr>
<tr>
<td><strong>Low-dose Warfarin vs. Placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginsberg et al. (2002) Canada</td>
<td>7 (RCT)</td>
<td>102 rehabilitating stroke patients were randomized to receive 2 mg of daily warfarin (or dose adjusted to maintain INR of ≤2) or placebo and followed for 120 days or until an event (DVT) had occurred. Patients were stratified into two groups: bedridden or wheelchair bound or walking with assistance.</td>
</tr>
<tr>
<td><strong>Anticoagulation and Antiplatelet Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harvey et al. (2004) USA</td>
<td>No Score</td>
<td>Analysis of a historical cohort of 1506 rehabilitating stroke patients to determine the effectiveness of anticoagulant and antiplatelet agents in preventing Fifty-eight VTE events occurred (3.9% incidence or 1.36 events per 1000 patient days), with higher risk in patients with severe stroke. Only</td>
</tr>
</tbody>
</table>
venous thromboembolism (VTE) during stroke rehabilitation. The use of anticoagulants (warfarin or anticoagulant doses of heparin), heparin in prophylactic doses, and antiplatelet agents was documented. The occurrence of deep vein thrombosis (DVT) detected by ultrasound or venography or pulmonary embolism detected by ventilation perfusion scan, spiral computed tomography, or pulmonary angiography was recorded.

therapeutic anticoagulation had a statistically significant protective effect for VTE risk (OR=.44; 95% CI, 0.20-0.98). After adjusting for multiple medication use and other factors, including age, stroke onset to admission interval, length of rehabilitation stay, cause of stroke, and stroke severity, therapeutic anticoagulation gave strong protection against VTE (OR=.37; 95% CI,15-.88), followed by heparin (OR=.48; 95% CI,.23-.98) but not by antiplatelet agents (OR=.79; 95% CI,40-1.57). No medications were associated with significant bleeding complications.

Discussion

Seven RCTs investigated the efficacy of anticoagulation therapy in reduction of DVT incidence when compared to a no-treatment placebo. McCarthy et al. (1986) found that subcutaneous heparin drastically reduced the likelihood of developing DVT when compared to a non-treatment control. Four studies compared low molecular weight (LMW) heparin to a placebo control group. The incidence of DVT were lower among patients in the treatment group in three of these trials (Kay et al. 1995; McCarthy & Turner 1986; McCarthy et al. 1977; Sandset et al. 1990; TOAST investigators 1998) although the TOAST investigators noted that patients in the LMWH group experienced a significantly greater number of major bleeds.

In two equivalency trials, Hillbom et al. (2002) and Diener et al. (2006) compared LMWH with unfractioned heparin (UFH). At the end of 3 months the incidence of DVT was lower among patients treated with enoxaparin (Hillbom et al. 2002) while there was no difference between groups in the PROTECT trial. The authors of the PROTECT trial suggested that the study results are not comparable since patients in the Hillbom trial were more disabled. The large international study, PEVAIL, comparing the LMWH enoxaparin with UFH delivered twice daily has just been completed. The authors concluded that enoxaparin is preferable to UFH in the prevention of DVT. The NNT associated to prevent one venous thromboembolism was 13. The number needed to harm as a result of a clinically significant bleed was 173. A recent meta-analysis evaluating the efficacy of LMWH and UFH included the results from these three trials (Shorr et al. 2008). The use of LMWH was associated with a significant risk reduction for either DVT or PE (OR: 0.54; 95% CI, 0.41 to 0.70; p < 0.001). Treatment with LMWH was also associated with a reduction in the incidence of proximal DVT (OR: 0.53; 95% CI, 0.37 to 0.75; p < 0.001) and PEs (OR: 0.26; 95% CI, 0.07 to 0.95; p = 0.042). There were no differences in rates of overall bleeding, intracranial hemorrhage, or mortality based on the type of agent employed.

A new agent, chemically related to LMWH, is Fondaparinux. It is a synthetic pentasaccharide that is an inhibitor of Factor Xa. While its efficacy is similar to that of enoxaparin, the side effect profile (major bleeding events) is believed to be superior and it has been associated with reduced mortality. Its use among stroke patients, specifically, has been evaluated in a single retrospective study (Mukand & Mukand 2010).

Two trials included aspirin as a treatment group (Bath et al. 2001; Berge et al. 2000). Both trials reported no differences in the incidence of DVT compared with LMWH. The TAIST investigators noted an increase in the risk of ICH in the LMWH group.
Pambianco et al. (1995) and Muir et al. (2000) did not report a decline in the incidence of DVTs among patients receiving a variety of treatments including electrical muscle stimulation, pneumatic compression and graded compression stockings. The results of the studies evaluating the efficacy of various drug treatments are presented in Tables 17.12 and 17.13.

### Table 17.12 Studies Evaluating Low Molecular Weight Heparin (LMWH) or Heparin vs. Placebo

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>PEDro Score</th>
<th>N</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kay et al. (1995)</td>
<td>7</td>
<td>312</td>
<td>High-does LMWH vs. low-dose LMWH vs. placebo</td>
<td>-</td>
</tr>
<tr>
<td>McCarthy et al. (1977)</td>
<td>5</td>
<td>32</td>
<td>Heparin vs. placebo</td>
<td>+</td>
</tr>
<tr>
<td>McCarthy and Turner (1986)</td>
<td>4</td>
<td>305</td>
<td>Heparin vs. placebo</td>
<td>+</td>
</tr>
<tr>
<td>Prins et al. (1989)</td>
<td>6</td>
<td>60</td>
<td>LMWH vs. placebo</td>
<td>+</td>
</tr>
<tr>
<td>Sandset et al. (1990)</td>
<td>8</td>
<td>103</td>
<td>LMWH vs. placebo</td>
<td>-</td>
</tr>
<tr>
<td>Turpie et al. (1987)</td>
<td>7</td>
<td>75</td>
<td>LMWH vs. placebo</td>
<td>+</td>
</tr>
<tr>
<td>TOAST (1998)</td>
<td>1281</td>
<td></td>
<td>LMWH vs. placebo</td>
<td>+ (at 3 months)</td>
</tr>
</tbody>
</table>

- Indicates a reduction in the incidence of DVT compared to placebo/alternative treatment
+ Indicates no difference in the incidence of DVT compared to placebo/alternative treatment

There are no studies of prophylaxis in stroke patients undergoing rehabilitation with all of the studies being in the acute stage. However, it is accepted use to maintain prophylactic heparin while the patient is at high risk, i.e. bedridden, in a wheelchair or where suffering from paralysis. Although clinically symptomatic DVTs are less common in the subacute (rehabilitation) phase, nevertheless Oczkowski et al. (1992) in a review of patients admitted to a stroke rehabilitation unit on average 60 days post-stroke, 11% had evidence of a DVT on IPG screening. The odds of having a DVT were 17.6 times greater if the patient was bedridden or wheelchair bound. There is currently no accepted stop date for the medication and prophylaxis is generally continued until the patient is ambulatory or until they are discharged from the rehab unit.
The combined odds ratio, using a random effects model for the incidence of DVT associated with heparin treatment or LMWH was 0.22 (95% CI 0.08 to 0.55) (See Figure 17.1).

**Figure 17.1 Forest Plot of the Effectiveness of Heparin or LMW Heparin vs. Placebo in Preventing DVT Following Stroke**

Andre et al. (2007) calculated the number needed to treat (NNT) to prevent one case of DVT following stroke associated with a variety of treatment approaches. The results are presented in Table 17.14.

**Table 17.14 NNTs Associated with DVT Prevention (Andre et al. 2007)**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>2-10</td>
</tr>
<tr>
<td>LMWH</td>
<td>1-4 (compared with placebo)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>9 (low dose fixed regimen 2 mg)</td>
</tr>
<tr>
<td>Mechanical methods</td>
<td>9-16</td>
</tr>
<tr>
<td>Aspirin</td>
<td>&gt; 300</td>
</tr>
</tbody>
</table>

**Alternative oral anticoagulation for treatment of DVT/PE:**

The oral direct thrombin inhibitor dabigatran was recently studied in a randomized, double-blind, noninferiority trial vs. Warfarin in the treatment of acute venous thromboembolism (Schulman et al. 2009). In this study, patients in both groups were initially treated with parenteral anticoagulation for a mean 10 days then either dabigatran 150mg twice daily or Warfarin dosed to INR between 2-3. There was no significant difference between groups with respect to recurrent DVT and both had similar safety profile with respect to major bleeding episodes and episodes of any bleeding. As a result, the study concluded that fixed dose dabigatran is as effective as warfarin for the treatment of acute venous thromboembolism and does not require laboratory monitoring.
The oral factor Xa inhibitor rivaroxaban has also been studied for the treatment of DVT (Investigators 2010) as well as PE (Investigators 2013). To study rivaroxaban’s efficacy in the treatment of acute, symptomatic DVT, an open-labeled noninferiority study was constructed comparing rivaroxaban (15mg twice daily for 3 weeks then 20mg once daily for a total of 6 months) to subcutaneous enoxaparin followed by a vitamin K antagonist (wither 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 (Investigators 2010). Regarding treatment of PE rivaroxaban (15mg twice daily for 3 weeks then 20mg once daily for a total of 6 months) was compared to subcutaneous enoxaparin followed by a vitamin K antagonist (wither warfarin or acenocoumarol). Again the two groups had similar rates of recurrence of PE however the rivaroxaban group had fewer episodes of major bleeding than the control (1.1% vs. 2.2% respectively, hazard ratio, 0.49;95% CI, 0.31 to 0.79; P=0.003).

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

Conclusions Regarding the Prevention of Deep Venous Thromboembolism

*There is strong (Level 1a) evidence that anticoagulation significantly reduces the incidence of deep venous thromboembolism, compared to placebo. Given the relatively benign nature of lower dose heparin it would seem prudent to recommend heparin for stroke patients with lower extremity paresis during hospitalization or at least for the first 14 days.*

*There is strong (Level 1a) evidence that low molecular weight heparin is better than unfractionated heparin in reducing hemorrhagic complications of associated with anticoagulant therapy and in decreasing the frequency of venous thromboembolism.*

*There is moderate (Level 1b) evidence that heparin is equivalent to both pneumatic compression and electrical stimulation in reducing the risk of DVTs.*

17.4.4 Prevention of DVT through Mechanical Methods

The use of physical forms of prophylaxis, including graded compression stockings (GCS) or TEDS has been questioned and debate continues over the risks and benefits of this treatment for stroke patients. The mechanism by which TED stockings reduce the risk of DVT is not entirely well-understood (Amaragiri & Lees 2000). Graduated compression stockings compress the surface veins, keeping their diameter small, and forcing blood into the deep vein system. GCS can accelerate the velocity at which the blood flows through the deep veins, which helps to relieve the symptoms associated with venous insufficiency. Although seen as a relatively benign intervention, their use has been associated with side effects as serious as skin ulceration and necrosis. A Cochrane review by Amaragiri and Lee (2000) suggests that there is a significant decrease in DVT risk among post-surgical patients who wore the stockings, although an RCTs involving stroke patients was not included in this review (Muir et al. 2000).

A Cochrane review authored by Naccarato et al. (2010) examined the effectiveness of the use of compression stockings and intermittent pneumatic compression devices among RCTs investigating stroke patients specifically. The review included five RCTs, two assessing intermittent pneumatic compression (IPC) devices and 3 assessing graded compression stockings (GCS). The use of either method was not associated with significant reductions in 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.

Since this Cochrane review, the CLOTS 3 study has been reported sheading new light into the possible role of intermittent pneumatic compression on DVT prevention (Collaboration 2013). The CLOTS (Clots in Legs Or sTockings after Stroke) 3 study investigated with effectiveness of IPC in the reduction of DVT risk using a large multicentre RCT. The 94 participating sites enrolled 2876 patients with acute stroke and resultant immobility to randomly receive IPC or no IPC within 3 days of stroke. A compression duplex ultrasound (CDU) of both legs at 7-10 days and again at 25-30 days or when symptomatic of DVT. The IPC was worn at all times for a minimum of 30 days (except for washing and therapy) or until the second screening. At the conclusion of the study, DVT was diagnosed in 122/1438 (8.5%) in the IPC group and 174/1438 (12.1%) in the no IPC group resulting in an absolute risk reduction of 3.6%. There was no significant difference between groups on secondary outcomes of death and falls with injury, however, there were more episodes of skin breakdown on the legs (IPC: 44 (3%) patients, No IPC: 20 (1%) patients, p=0.002). This large study provides some support for the use of IPC in DVT prevention, however when used the treating team must continually screen for skin injury and possible ulcer formation.

<table>
<thead>
<tr>
<th>Author, Year Country PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prasad et al. (1982) USA 5 (RCT)</strong></td>
<td>26 acute stroke patients with weakness in either one or both limbs were randomized to receive intermittent pneumatic calf compression for 9 days or to a no treatment control group. DVT was assessed by I-25 Fibrinogen test.</td>
<td>There were no significant differences in the development of DVT between the groups at day 10. Six patients in each group had a positive scan, although clinical signs of DVT were only noted in one person with a positive scan.</td>
</tr>
<tr>
<td><strong>Muir et al. (2000) UK 7 (RCT)</strong></td>
<td>98 stroke patients who were not independently ambulatory within 24 hours of admission were randomized to receive either standard care (control), which included aspirin or early mobilization (n=32) or standard care plus TED or Brevett (TX) brand stockings (n=65). The thighs and calves of both legs were examined at baseline and again at day 7, using Doppler ultrasound.</td>
<td>DVT was detected in 7/65 patients allocated stockings, and 7/32 controls, which was associated with an overall reduction in the odds of DVT (odds ratio 0.43, 95% CI 0.14-1.36). The absolute risk of developing proximal DVT was 6.25% in controls and 4.6% in the stocking group.</td>
</tr>
<tr>
<td><strong>Lacut et al. (2005) VICTORIAh France 7 (RCT)</strong></td>
<td>151 acute patients with intracerebral aemorrhage were randomly assigned to treatment with TED brand stockings (n=77) or TED+ intermittent pneumatic compression (IPC) device.</td>
<td>At day 10 of treatment 11 patients in the TED group experienced an asymptomatic DVT (3 proximal, 8 distal) compared with 3 in the TED+ICP group. Absolute risk reduction was 11%. At the end of 3 months, 2 patients, one in each group experienced a symptomatic VTE. None of the 14 deaths were attributable to PE.</td>
</tr>
<tr>
<td><strong>CLOTS (1) (2009) UK 8 (RCT)</strong></td>
<td>2,518 patients, admitted to hospital within 1 week of an acute stroke and who were immobile were enrolled from 64 centres in the UK, Italy, and Australia. Patients randomized to either routine care plus thigh-length GCS (n=1256) or to routine care plus avoidance of GCS (n=1262). Doppler ultrasound of both legs was performed at about 7-10 days and, when practical, again at 25-30 days after enrolment. The primary outcome was the occurrence of DVT.</td>
<td>DVT occurred in 126 (10.0%) patients allocated to thigh-length GCS and in 133 (10.5%) allocated to avoid GCS, resulting in a non-significant absolute reduction in risk of 0.5% (95% CI -1.9% to 2.9%). Adverse effects (skin breakdown, necrosis, ulcers) were significantly more common in the GCS group.</td>
</tr>
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</table>
of symptomatic or asymptomatic DVT in the popliteal or femoral veins.

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOTS (2) (2011) UK 6 (RCT)</td>
<td>3,114 acute, immobile stroke patients from 112 centres were randomized to 1552 patients to wear thigh-length stockings (n=1552) or below-knee stockings (1562) while they were in the hospital, in addition to routine routine care, which could have included early mobilization, anticoagulants etc. The primary outcome measure was symptomatic or asymptomatic proximal DVT, assessed by compression duplex ultrasonography at either first (days 7-10) or on a second scan at day 30.</td>
<td>The incidence of proximal DVT within 30 days was significantly higher in the below-knee stocking group compared with the above keen group (8.8% vs. 6.3%, p=0.008). The associated odds reduction was 31% (CI, 9% to 47%). Seventy-five percent of patients in both groups wore the stockings for 30 days or until they were discharged, died, or regained mobility.</td>
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<tr>
<td>CLOTS (3) (2013) UK 6 (RCT)</td>
<td>2876 acute, immobile stroke patients from 94 centres were randomized to 1438 to wear intermittent pneumatic compression (IPC) or 1438 to no IPC while they were in hospital. The IPC was provided within 3 days of stroke and worn at all times except for washing and therapy. Anticoagulant prophylactic use was similar between groups for limited to only 17% of patients. The primary outcome measure was symptomatic or asymptomatic proximal DVT, assessed by compression duplex ultrasonography at either first 7-10 days or on second scan at 25-30 days</td>
<td>The incidence of DVT within 30 days was lower in the IPC group compared to no IPC (8.5% vs. 12.5%, ARR 3.6% (95% CI 1.4-5.8). There were 156 deaths in the IPC group (11%), and 189 (13%) in the no IPC group (p=0.057). Falls with injury were reported in 33 participants (2%) in the IPC group and 24 (2%) in the no IPC group (p=0.221). Skin breaks were reported in 44 individuals (3%) in IPC group and 20 (1%) in the no IPC group (p=0.002).</td>
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</table>

Neither Muir et al. (2000) or Prasad et al. (1982) reported differences in the development of DVT between groups in their small studies evaluating two different treatment approaches. The results from the largest and most methodologically rigorous trial to date CLOTS (1) suggests that there is no decreased risk of developing a DVT within 30 days of stroke associated with use of thigh-length graduated compression stockings. In fact, there was an increase in the number of adverse events reported with the use of stockings. However, the results from the CLOTS 2 trial indicated that the incidence of DVT was higher among patients randomized to wear knee-length GCS compared with those who wore thigh-length stockings. Although the results of each of these studies are clear and simple to understand, when combined, they are hard to interpret. The authors suggested that the use of knee-length stocking may actually increase the risk of DVT or that the protective effect of thigh-length stockings may have been under-estimated in the CLOTS 1 trial.

The prevention of DVT among patients suffering from ICH can be problematic given that traditional anticoagulants are hazardous to patients already at increased risk for bleeding complications. The VICTORIA investigators found that a combination of TED stocking and IPC was more effective than TED stockings alone for preventing asymptomatic DVT. There were no cases of symptomatic DVT in either group during the study period. However, a significant percentage (19%) did not tolerate treatment with ICP well and stopped using it within 5 days.

**Conclusions Regarding the Prevention of Deep Venous Thromboembolism through Non-Pharmacological Means**

*There is conflicting (Level 4) evidence that graded compression stockings reduce the risk of proximal DVT.*

*There is strong (Level 1a) evidence that intermittent pneumatic calf compression devices reduce the risk of the development of DVTs.*
There is moderate (Level 1b) evidence that thigh-length graded compression stockings reduce the risk of proximal DVT compared with knee-length stockings.

17.5 Seizures Post Stroke

Post stroke seizures may occur soon after stroke or be delayed; each appears to be associated with differing pathogeneses. Most seizures are single, either partial or generalized (Ferro & Pinto 2004). Wiebe and Butler (1998) noted that, “Seizures are the clinical expression of excessive, hypersynchronous discharge of neurons in the cerebral cortex.” Whether seizures worsen outcome remains unclear. Vernino et al. (2003) reported new-onset seizure among patients with ischemic stroke was an independent risk factor for mortality (Relative risk 1.81; 95%CI 1.16-2.83). Bladin et al. (2000) also reported higher mortality among patients with seizures at 30 days and 1 year, compared to patients who were seizure free (25% vs. 7% and 38% vs. 16%). However, the authors did not control for the confounding effects of stroke severity or comorbidity. Similarly, higher mortality risk at 30 days and 1 year was seen in patients with early seizures but the risk disappeared after adjusting for stroke severity and other confounding factors (Hamidou et al. 2013). The results of other studies have also not supported an increased risk of mortality (Labovitz et al. 2001; Reith et al. 1997).

17.5.1 Incidence of Post Stroke Seizures

Wiebe and Butler (1998) observed that the incidence of seizures following ischemic or hemorrhagic stroke in earlier series is noted to be highly variable ranging from a low of 7.7% to a high of 42.8%. This variability tends to be influenced by factors such study design, patient population, diagnostic methods, and follow-up (Black et al. 1983; DeReuck et al. 1980; Dodge et al. 1954; Holmes et al. 1980; Louis & McDowell 1967; Meyer et al. 1971). Weibe and Butler (1998) suggest that high-resolution imaging such as with computed tomography (CT) and magnetic resonance imaging (MRI) has improved the ability to identify and classify strokes, resulting in better estimates of their clinical course and consequences.

In comparison to earlier studies, recent reports reveal less variability in the risk of post-stroke seizures (PSS). The average risk of seizures is 10% within 9-10 years after stroke (Table 17.10), and well-conducted prospective studies report a 5-year cumulative incidence of 11.5% (Burn et al. 1997). At least two studies suggest a higher incidence of PSS (15-17%) in patients in rehabilitation units (Kotila & Waltimo 1992; Paolucci et al. 1997). It is not certain whether this reflects seizure ascertainment bias (e.g., seizures are less likely to be missed in closely observed patients), or a true increased seizure risk in this population (e.g., more extensive cerebral injury) or both. Also, Cordonnier et al. (2005) reported that pre-existing dementia increase the risk of late seizures defined as greater than one week post-stroke.

Black et al. (1983) reported 10% of all stroke patients developed seizures. Thirty-nine percent of seizures occurred within the first 24 hours of stroke onset, 57% within the first week and 88% within the first year. Sung and Chu (1989) demonstrated that for patients with intracerebral hemorrhages, seizure onset time was very similar to that reported for other stroke entities; 30% in the first 24 hours, 60% in the first two weeks and 90% in the first year. Sundaram and Chow (1986) reported that in subarachnoid haemorrhage (SAH) patients, 84% of PSS took place within the first 2 weeks of stroke onset.

Table 17.16 The Prevalance and Incidence of Seizures Post Stroke

<table>
<thead>
<tr>
<th>Author, Year Country</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
</table>

17. Medical Complications Post Stroke

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<table>
<thead>
<tr>
<th>PEDro Score</th>
<th>Medical Complications Post Stroke</th>
<th>Evidence-Based Medical Complications Post Stroke</th>
<th>Evidence-Based Medical Complications Post Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Holmes et al. (1980)</strong>&lt;br&gt;USA&lt;br&gt;No Score</td>
<td>A retrospective study of 250 strokes patients who had an EEG within a week of their cerebral infarction and at least a 2 year follow up. EEGs were reviewed and classified into 1 of 4 categories (I: normal, II: diffuse slowing, III: focal slowing, and IV: sharp waves) and seizures were classified as early (within 1 month post-stroke) or late (after 1 month).</td>
<td>21% of patients had seizures at time of cerebral infarction or in the 2 year follow up. 8 out of 23 with early seizures and 6 of 20 with late seizures had initial EEGs in class IV. All patients with periodic lateralizing epileptiform discharges (PLEDs) on their initial EEGs developed seizures. Only 2% of those seizure-free had EEGs in class IV.</td>
<td></td>
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<tr>
<td><strong>De Reuck et al. (1980)</strong>&lt;br&gt;Belgium&lt;br&gt;No Score</td>
<td>Of 240 patients with cerebral infarcts at necropsy, during the years 1970 to 1979, 14 with clinical history of epilepsy were selected. Etiology of seizures was analyzed by comparing the clinical and pathological data.</td>
<td>Convulsive disorder was noted in 7.9% of patients with cerebral infarcts in study patients.</td>
<td></td>
</tr>
<tr>
<td><strong>Black et al. (1983)</strong>&lt;br&gt;Canada&lt;br&gt;No Score</td>
<td>Clinical data was prospectively collected on 827 patients with completed stroke.</td>
<td>10% of patients had seizures during their first admission or during 2 to 5 years follow-up. Seizures occurred only in those patients with hemispheric lesions. 39% of seizures occurred by the first day, 57% occurred by the first week and 88% occurred by the first year.</td>
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<tr>
<td><strong>Olsen et al. (1987)</strong>&lt;br&gt;Denmark&lt;br&gt;No Score</td>
<td>Development of epilepsy studied prospectively in a sample of 77 stroke patients less than 75 years old admitted within first 3 days of onset. Cerebral angiography, CT and EEG were performed in all patients clinically followed for 2 to 4 years.</td>
<td>9% of patients developed epilepsy. Of 23 with lesions involving the cortex, 6 developed epilepsy and of the 54 patients that had no cortical involvement, only 1 developed epilepsy. 50% of patients with persisting paresis and cortical involvement developed epilepsy.</td>
<td></td>
</tr>
<tr>
<td><strong>Gupta et al. (1988)</strong>&lt;br&gt;USA&lt;br&gt;No Score</td>
<td>Retrospectively studied 90 patients with post infarction seizures to determine the clinical features, prognosis and electroencephalographic computed tomographic findings.</td>
<td>33% of the 90 seizures appeared within 2 weeks after infarction and 90% of the early seizures appeared within 24 hours after then infarction. 73% of seizures occurred within the first year and only 2% occurred after the 2 years. The most common electroencephalographic abnormality was focal slowing by recurrent seizures occurred in all patients with periodic lateralized epileptiform discharges and in 75% of patients with diffuse slowing. CT scan showed large infarctions were associated with early and multiple seizures. Deep infarctions on CT tended to cause recurrent seizures.</td>
<td></td>
</tr>
<tr>
<td><strong>Vittanen et al. (1988)</strong>&lt;br&gt;Sweden&lt;br&gt;No Score</td>
<td>Analyzed the risk of recurrent stroke, myocardial infarction and epilepsy in a population-based cohort of 409 stroke patients over 3.5 to 7 years.</td>
<td>The risk of epilepsy was 3±2% at 1 year and 5±4% at 5 years.</td>
<td></td>
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<tr>
<td><strong>Kotila &amp; Waltimo (1992)</strong>&lt;br&gt;Finland&lt;br&gt;No Score</td>
<td>A retrospective follow-up of 200 stroke patients who were in need of ambulatory rehabilitation after stroke for a mean period of 40 months.</td>
<td>Epilepsy developed in 33 (17%) patients. The occurrence of epilepsy was 14% in IBI, 15% in ICH and 35% in SAH. 15% of those developing seizures did so within first 2 weeks and 55% developed epilepsy in first 6 months post-stroke. 48% were generalized seizures and antiepileptic drug (AED) treatment was started in 28 of 33 patients.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Score</td>
<td>Study Design</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------</td>
<td>-------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Lancman et al. (1993)</td>
<td>USA</td>
<td>No Score</td>
<td>Evaluated the development of seizures in 219 consecutive patients who had ischemic or hemorrhagic stroke for a period of 11.5 months.</td>
</tr>
<tr>
<td>So et al. (1996)</td>
<td>USA</td>
<td>No Score</td>
<td>Performed a population-based study determining the risk and factors predictive of developing seizures after stroke on 535 stroke patients without prior unprovoked seizures. Patients were followed until death or until migration out of the catchment area (Rochester, MN).</td>
</tr>
<tr>
<td>Burn et al. (1997)</td>
<td>UK</td>
<td>No Score</td>
<td>A cohort follow-up study on 675 first-time stroke patients.</td>
</tr>
<tr>
<td>Paolucci et al. (1997)</td>
<td>Italy</td>
<td>No Score</td>
<td>A prospective study of 306 first-time stroke patients assessed at discharge and at 1-year follow-up.</td>
</tr>
<tr>
<td>Teasell et al. (1999)</td>
<td>Canada</td>
<td>No Score</td>
<td>A retrospective review. 563 stroke rehabilitation patients were evaluated for seizures for 1 year.</td>
</tr>
<tr>
<td>Bladin et al. (2000)</td>
<td>Australia</td>
<td>No Score</td>
<td>A multicentred prospective evaluation of the incidence, outcome, and risk factors for seizures after stroke.</td>
</tr>
<tr>
<td>Study</td>
<td>Authors (Year)</td>
<td>Country</td>
<td>Score</td>
</tr>
<tr>
<td>-------</td>
<td>---------------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>Lossius et al. (2002)</td>
<td>Norway</td>
<td>No Score</td>
<td>Prospective study of 550 patients followed for one year to determine the incidence of post stroke epilepsy (defined as 2 or more unprovoked epileptic seizures occurring at least 4 weeks following stroke).</td>
</tr>
<tr>
<td>Vespa et al. (2003)</td>
<td>USA</td>
<td>No Score</td>
<td>109 patients with ischemic stroke (n = 46) and intraparenchymal hemorrhage (n = 63) prospectively underwent continuous EEG monitoring after admission.</td>
</tr>
<tr>
<td>Cordinnier et al. (2005)</td>
<td>France</td>
<td>No Score</td>
<td>Prospective systematic study of 202 consecutive stroke patients evaluated for dementia at 6 months follow-up and then every year for 3 years.</td>
</tr>
<tr>
<td>Alberti et al. (2008)</td>
<td>Italy</td>
<td>No Score</td>
<td>638 consecutive patients with first-ever stroke (543 ischemic, 95 hemorrhagic) admitted to an acute stroke unit were included and monitored for early seizures (ES). Patients with history of epilepsy were excluded. ES were defined as seizures occurring within 7 days from acute stroke.</td>
</tr>
<tr>
<td>Szaflarski et al. (2008)</td>
<td>USA</td>
<td>No Score</td>
<td>The incidence of seizure within 24 hours of event was determined among a population-based cohort of patients admitted to hospital for stroke during a 3-year period. Patients with a prior history of seizures/epilepsy were excluded.</td>
</tr>
<tr>
<td>Burneo et al. (2010)</td>
<td>Canada</td>
<td>No Score</td>
<td>The data from 5027 patients included in the Registry of the Canadian Stroke Network between 2003 and 2005 were examined to identify the incidence of seizure during inpatient stay. Patient with both ischemic and hemorrhagic stroke were included.</td>
</tr>
<tr>
<td>Krakow et al. (2010)</td>
<td>Germany</td>
<td>No Score</td>
<td>The incidence of seizure was obtained from a large hospital-based stroke registry in Germany. 58,874 patients with the diagnosis of TIA, ischemic stroke (IS) or intracerebral hemorrhage (ICH) were included.</td>
</tr>
<tr>
<td>Beghi et al. (2011)</td>
<td>Italy</td>
<td>No Score</td>
<td>714 patients with first stroke from 31 Italian centers were recruited. 609 (85.3%) patients had cerebral</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study Type/Source</td>
<td>N</td>
<td>Prevalence of Seizures</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------</td>
<td>-------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Stirling et al. 1971</td>
<td>Prospective</td>
<td>42</td>
<td>42.8%</td>
</tr>
<tr>
<td>Holmes et al. 1980</td>
<td>Retrospective</td>
<td>250</td>
<td>21%</td>
</tr>
<tr>
<td>de Reuck et al. 1980</td>
<td>Retrospective</td>
<td>240</td>
<td>7.9%</td>
</tr>
<tr>
<td>Black et al. 1983</td>
<td>Prospective</td>
<td>827</td>
<td>10% (5.7% in 1st week)</td>
</tr>
<tr>
<td>Olsen et al. 1987</td>
<td>Prospective</td>
<td>77</td>
<td>9%</td>
</tr>
<tr>
<td>Viltanen et al. 1988</td>
<td>Prospective</td>
<td>409</td>
<td>3% @ 1 year and 5% @ 5 years</td>
</tr>
<tr>
<td>Kotila &amp; Waltimo 1992</td>
<td>Retrospective</td>
<td>200</td>
<td>17%</td>
</tr>
<tr>
<td>Lanceman et al. 1983</td>
<td>Prospective</td>
<td>219</td>
<td>10%</td>
</tr>
<tr>
<td>So et al. 1996</td>
<td>Retrospective</td>
<td>535</td>
<td>6%</td>
</tr>
<tr>
<td>Burn et al. 1997</td>
<td>Prospective</td>
<td>675</td>
<td>7.7%</td>
</tr>
<tr>
<td>Paoluccio et al. 1997</td>
<td>Prospective</td>
<td>306</td>
<td>15%</td>
</tr>
<tr>
<td>Teasell et al. 1999</td>
<td>Retrospective</td>
<td>536</td>
<td>7.8%</td>
</tr>
<tr>
<td>Bladin et al. 2000</td>
<td>Prospective</td>
<td>1897</td>
<td>8.9%</td>
</tr>
<tr>
<td>Lossius et al. 2002</td>
<td>Prospective</td>
<td>550</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

**Discussion**

The occurrence of post stroke seizures varies between 5% to 43%; or 10% on average. Seizures usually occur during the first 1 to 2 weeks following stroke. Consequently, a majority of seizure events will have already occurred before the patient is admitted to the stroke rehabilitation unit.
Early vs. Late Seizures

Seizures can occur either during the acute phase or during the following months after stroke (Procaccianti et al. 2012). There is a lack of consistency among studies when describing the differences in timing of onset between early and late onset seizures. Early seizures have been defined as those occurring within 24 hours of stroke onset to as late as one month following stroke, while late seizures are most commonly identified as those occurring after two weeks of stroke. The incidence of seizures grouped according to time following stroke is presented in Table 17.17.

**Table 17.17 Frequencies and Timing of Seizures Post Stroke (adapted from Camilo & Goldstein 2004)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Incidence of seizure (Study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 24 hours</td>
<td>2% (Burn et al. 1997) (3% after 24 hours)</td>
</tr>
<tr>
<td>&lt; 48 hours</td>
<td>2.2% (Arboix et al. 2003)</td>
</tr>
<tr>
<td>&lt; 1 week</td>
<td>2.4% (Lamay et al. 2003) (3.4% after 1 week)</td>
</tr>
<tr>
<td></td>
<td>3.1% (Labovitz et al. 2001)</td>
</tr>
<tr>
<td></td>
<td>6% (So et al. 1996) (5% after 1 week)</td>
</tr>
<tr>
<td></td>
<td>3.2% (Procaccianti et al. 2012)</td>
</tr>
<tr>
<td></td>
<td>3.9% (Pezzini et al. 2013)</td>
</tr>
<tr>
<td>&lt; 2 weeks</td>
<td>4.8% (Bladin et al. 2000, Alberti et al. 2008) (3.8% after 2 weeks)</td>
</tr>
<tr>
<td></td>
<td>6.5% (Kilpatrick et al. 1990)</td>
</tr>
<tr>
<td></td>
<td>33% (Gupta et al. 1998) (67% after 2 weeks)</td>
</tr>
<tr>
<td></td>
<td>4.2% (Reith et al. 1997)</td>
</tr>
<tr>
<td></td>
<td>3.1% (Hamidou et al. 2013)</td>
</tr>
</tbody>
</table>

Risk Factors Associated with Seizures

The results from two studies suggest that both younger patients and men are at increased risk for seizure activity post stroke (Arboix et al. 1997; Giroud et al. 1994). Loss of consciousness, a confusional state and paresis have been associated with seizures following stroke (Arboix et al. 1997; Giroud et al. 1994; Reith et al. 1997). Lamy et al. (2003) identified three independent risk factors for late onset seizures: early acute seizures, cortical signs and large strokes. These risk factors were associated with a 4.5-10-fold increase in the risk of late onset seizures. Bladin et al. (2000) noted that patients who had suffered from a hemorrhagic stroke had an almost 2-fold risk of developing a seizure following stroke compared to patients with an ischemic lesion. Cortical location was the only risk factor identified for seizure among patients with hemorrhagic stroke. Among patients with ischemic stroke, disability and cortical location were both identified as risk factors. In the Copenhagen Stroke Study, Reith et al. (1997) also identified stroke severity as the single biggest risk factor for early seizures. In two of the largest, population-based studies included in this review younger age and increasing stroke severity were found to be predictors of seizures following stroke occurring within 24 hours (Krakow et al. 2010; Szaflarski et al. 2008). Recently, thrombolysis has been identified as an independent risk factor for seizure. In a population-based case-control study including n=2,327 ischemic stroke patients, the overall incidence of seizure was 1.2% (Alvarez et al. 2013). The odds of seizure among patients who had received thrombolytic therapy was increased significantly (OR=4.6, 95% CI 1.6 to 13.4) in multivariable analysis. Cortical involvement was also identified as an independent predictor. The authors speculated that
neurotoxicity was the most plausible cause associated with the increased risk. In a cohort of Canadian stroke patients included in the Registry of the Canadian Stroke Network (Burneo et al. 2010), stroke severity, hemorrhagic stroke and neglect were found to be independent predictors of seizure during the initial period of hospitalization following stroke.

**Conclusions Regarding the Incidence of Seizures Post Stroke**

*The occurrence of post-stroke seizures varies widely among studies. Approximately 10% of patients experienced seizure activity within the first two years following stroke.*

**Approximately 10% of stroke patients experience seizures.**

17.5.2 Seizures Following Hemorrhagic Stroke

The incidence of seizure following hemorrhagic stroke is estimated to be between 4% and 16% (DeHerdt et al. 2011). Seizure incidence for subarachnoid hemorrhagic patients has been found to be as high as 24% (Sundaram & Chow 1986). The results from some studies support the theory 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), while others do not (Alberti et al. 2008; Black et al. 1983; Olsen et al. 1987; Shinton et al. 1988). Chen et al. (2012) noted that the adjusted hazard ratio for developing post stroke seizure after 5 year follow-up was highest for the intracerebral hemorrhage (ICH) [HR 76.3 (95% CI: 17.1 to 329.5)], compared to subarachnoid hemorrhage [HR 9.0 (95% CI 1.6 to 50.5)], and lowest in ischemic stroke [6.8 (95% CI: 4.4 to 10.5)].

Reith et al. (1997) found a higher frequency of early seizures (within 14 days of onset) in patients with intracerebral hemorrhages when compared to those with cerebral infarction. However, in multivariate analysis, initial stroke severity was the sole predictor of early PSS and the apparent increased frequency of PSS with intracerebral hemorrhage reflected a higher initial stroke severity in this group of patients.

17.5.3 Seizures in Cortical vs. Subcortical Strokes

The results of some studies showed that PSS only occurred in patients with cortical involvement (Kilpatrick et al. 1990; Lancman et al. 1993) while others did not (Gupta et al. 1988; Shinton et al. 1988). Olsen et al. (1987) found that a lesion involving the cerebral cortex, irrespective of size, was a prerequisite for the development of epilepsy. Kilpatrick et al. (1990) supported this concept by reporting 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). Although Alberti et al. (2008) reported, on univariate analysis, that early seizures occurred more frequently in patients with cortical involvement (58.1% vs. 33.2%, p=0.01) the association disappeared when controlling for other variables.

17.5.4 Seizure Type Post Stroke

Wiebe-Velazquez and Blume (1993) totalled the frequency of various seizure types following stroke from seven studies. From the combined 231 patients, the overall percentage of focal seizures was 50%, generalized seizures 32%, focal seizures with secondary generalization 15% and complex partial seizures 2.5%.
17.5.5 Treatment of Post-Stroke Seizures

There have been few studies of the treatment of seizures post stroke and no definitive evidence recommending one treatment over another. Clinical guideline are often based on established management of seizures in other types of epilepsy (Gilad 2012). Standard first-line therapy usually includes carbamazepine, valproic acid and phenytoin sodium. However, phenytoin is known to interact with warfarin, a commonly prescribed drug for patients who have suffered from a cardioembolic stroke. There is some concern that the use of antiepileptic agents may impair recovery post stroke (Camilo & Goldstein 2004), which should be a consideration in the decision of whether to treat an isolated seizure. The newer anti-epileptic drugs such as lamotrigine may be better tolerated and have a better side-effect profile than some of the older drugs. Benzodiazepines as an ongoing treatment should be avoided unless seizure activity is uncontrolled due to its sedating effects.

Both lorazepam and diazepam given intravenously are equally acceptable acute treatment strategies, although lorazepam may be more effective in terminating status epilepticus (59-89% vs. 43-76%). Intravenous lorazepam is the preferred first line agent for seizure control due to its long lasting anticonvulsant properties. Lorazepam lasts 12 hours versus 20 minutes for diazepam, which places patients at risk of seizure recurrence unless a longer acting drug is given (Bluvol & K. 2003).

A Cochrane review (Kwan & Wood 2010) attempting to examine the efficacy of antiepileptic drugs for either the prevention or treatment of seizure following stroke found no studies which met criteria for inclusion in the review. The authors concluded that there is insufficient evidence to support the use of antiepileptic drugs for the management of post-stroke seizures. Five studies were described but all the studies were excluded based on the absence of a placebo or no drug control group.

Table 17.18 The Treatment or Prevention of Seizures Post Stroke

<table>
<thead>
<tr>
<th>Author, Year Country PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alvarez-Sabin et al. (2002)</strong></td>
<td>The long-term efficacy and tolerability of gabapentin (900 to 1,800 mg/day) was evaluated in 71 patients (ischemic stroke=48, hemorrhagic stroke=23) with a first post-stroke late seizure. The mean follow-up period was 30 months.</td>
<td>Seizure recurred in 13 (18.3%) patients over the study period. 7 patients died. Side effects were noted in 27 cases (38%), but only two (2.8%) required discontinuation or early withdrawal.</td>
</tr>
<tr>
<td><strong>Rowan et al. (2005)</strong> USA 9 (RCT)</td>
<td>593 elderly subjects with newly diagnosed seizures from 18 centres were randomly assigned to one of three treatment groups: lamotrigine (LTG) 150 mg/day, gabapentin (GBP) 1,500 mg/day, and carbamazepine (CBZ) 600 mg/day for up to 12 months. The most common etiology of seizure was ischemic stroke (51%).</td>
<td>276 (46.8%) completed 1 year in trial. Patients in the CBZ group were more likely to terminate the study early compared with patients in the GBP or LTG groups. At 3, 6 and 12 months, 63.2%, 58.6% and 53.3% patients remained seizure free. There were no differences across treatment groups in terms of efficacy.</td>
</tr>
<tr>
<td><strong>Gilad et al. (2007)</strong> Israel 3 (RCT)</td>
<td>64 patients with a first post episode of seizures were randomized to receive either lamotrigine (LTG) or carbamazepine (CBZ) treatment. Subjects were followed for up to 12 months to establish efficacy and tolerability of the drugs.</td>
<td>At 12 months more patients in the LTG group were seizure-free (72%) versus those in the CBZ group (44%), although the result was not statistically significant (p = 0.06). Fewer subjects withdrew due to side-effects in the LTG group (3%) compared with the CBZ group (31%; p = 0.02).</td>
</tr>
<tr>
<td><strong>Van Tuijl et al.</strong> Stroke patients with a cortical syndrome</td>
<td>Recruitment began in 2005. Over 16 months, only 16 patients</td>
<td></td>
</tr>
</tbody>
</table>
The ETLAS trial (Early Treatment with Levetiracetam After Stroke for the prevention of seizures) by van Tuijl JH et al. (2011) was initiated aiming to determine whether treatment with levetiracetam vs placebo is effective in the prevention of post stroke seizure. The trial did not meet the intended sample size due to various factors. The authors concluded that a prophylactic trial in stroke patients aimed at preventing poststroke seizures and epilepsy is not feasible and no conclusion can be drawn (van Tuijl et al. 2011). Future trials examining the use of medications for the prevention of stroke are unlikely to be initiated. Only a single RCT (Gilad et al. 2007) has been conducted to evaluate the efficacy of anticonvulsant therapy in which one treatment was compared with another (lamotrigine vs carbamazepine). Although the results were not statistically significant, the small sample size may have masked a real treatment effect of lamotrigine. Lamotrigine may be a better treatment option compared with carbamazepine since lamotrigine is more tolerable, has relatively few side-effects, fewer potential drug interactions and does not require blood monitoring in monotherapy. It is generally recommended that initiation of antiepileptic medications after a first or second post stroke seizure be individualized (Gilad 2012).

### Conclusions Regarding the Treatment of Post-Stroke Seizure.

There is no significant difference on the efficacy of any antiepileptic in the management of post stroke seizure. Lamotrigine may be preferred due to relatively less side effects and drug interactions.

There is consensus (Level 3) opinion that patients who have experienced seizures post stroke should be given preventative anticonvulsant medication to prevent seizure reoccurrence.

No evidence exist for prophylactic measure to prevent early post stroke seizure.

The treatment of seizures post stroke has not been well studied. There is no significant difference in the efficacy of any antiepileptic in the management of post stroke seizure.
17.6 Osteoporosis Post Stroke

17.6.1 Hip Fractures

“Osteoporosis is a significant complication of stroke, and hip fracture after stroke is a frequent problem” (Saverino et al. 2006). The incidence of hip fracture as a late complication of stroke, caused by a loss of bone mineral density, resulting in falls, has been reported to be 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). Moreover, Watanabe (2004) found that 40% of patients admitted for inpatient stroke rehabilitation already had osteoporosis. Ramnemark et al. (1998) reported the risk of hip fracture to be 2-4 times higher among stroke survivors compared to the general population among 1139 patients followed for a median of 2.9 years. Most post stroke fractures are caused by accidental falls (Poole et al. 2002). The higher risk appears to be related to bone density at the hip and the ability of the ipsilateral hand to outstretch and cushion the fall. Advanced age, female gender, prestroke use of body image, low abbreviated mental test score and diabetes mellitus are also known to be independent risk factor for both hip fracture and stroke (Dennis et al. 2002; Ishida et al. 1985; Kanis et al. 2001). Additional risk factors include depression, poor balance, urinary incontinence and medications (Eng et al. 2008). Hemineglect and attention deficits may also increase the risk of falling post stroke. Kanis et al. (2001) reported a 7-fold increase in hip fracture in the first year following stroke. This increased risk has been attributed to the development of disuse osteoporosis following stroke and to perceptual deficits and balance disorders that predispose patients to falling (Peszczynski 1956). In addition, Beaupre and Lew (2006) noted that patients with hip fracture had a considerable increase in risk of morbidity and mortality following stroke.

17.6.2 Pathophysiology of Osteoporosis Following Stroke

Reduced bone mineral density associated with prolonged immobility has been previously documented in spinal cord injury patients (Claus-Walker et al. 1975; Naftchi et al. 1980). During the first year following stroke, subjects can lose from 14% to 17% of their bone mineral density (Carda et al. 2009). Vitamin D deficiency, induced through inadequate dietary intake and sunlight deprivation as well as compensatory hyperparathyroidism may also be contributory (Sato et al. 1999). Associations between the ability to ambulate independently and bone mineral density (BMD) in stroke patients highlights the importance for screening patients for bone loss (Schnitzer et al. 2012). Unfortunately, few stroke management guidelines include recommendations regarding bone loss or osteoporosis (Borschmann 2012). There is a large amount of evidence to suggest that loss of bone mineral density is greater on the hemiparetic side relative to the non-affected side (Beaupre & Lew 2006; De Brito et al. 2013; Demirbag et al. 2005; Hamdy et al. 1993; Jorgensen et al. 2000; Liu et al. 1999; Ramnemark et al. 1999; Sato et al. 1996; Yavuzer et al. 2002), even with no significant change in overall stroke impairment variables (spasticity, disuse, etc.) (Pang et al. 2013). Beaupre and Lew (2006) found that for some patients the loss of bone density in the affected arm within the first year post-stroke is equal to more than 20 years of bone loss for similar aged healthy individuals. Hamdy et al. (1993) reported a significant percentage difference in bone mineral density and content for the affected upper limb 13.8% (p<0.00001) compared to the nonaffected upper limb 7.95% (p=0.0003) and for the affected lower limb 4.5% (p=0.0012) in comparison to the nonaffected lower limb 3.42% (p=0.0028) of stroke patients. In stroke patients with chronic hemiplegia (i.e. > 12 months), de Brito et al. (2013) found that the mean change in forearm bone mineral density (BMD) was greater on the paretic than on the nonparetic side, although for each additional month since stroke less ΔBMD was found (indicating ΔBMD tends to stabilize over time). In addition, Lui et al. (1999) noted that “age, sex, duration of stroke, anthropometric
measurements, motor paralysis, muscle strength, and activity level contributed differently to bone loss according to the sit and timing of the measurement”.

Immobilation leads to increased bone resorption, leading to hypercalcemia. Calcium released from the bone is excreted in the urine (hypercalciuria). Renal synthesis of 1,25 dihydroxycolcalciferol (calcitriol) is therefore inhibited, mediated through decreased parathyroid hormone, decreasing calcium absorption from the gut (Massaglì & Cardenas 1999). These processes all favour reduction of bone formation. Sato et al. (1998) reported that bone loss continued for one-year after hemiplegic stroke and returned to the normal range after the second year. They also reported decreased metacarpal bone mass in hemiplegic limbs (Sato et al. 1998). The determinants of bone loss include the duration of immobility, degree or severity of hemiplegia and time since menopause in women (Poole et al. 2002). Levendoglu et al. (2004) also described how decreased mobility, vitamin D status, and bone turnover variables could contribute to greater bone loss in the paretic leg in their study, which evaluated 80 stroke patients and 20 age-matched controls. Hamdy et al. (1993) reported that a significant side to side variation in arm vs. leg variation (12.4 vs. 4.3%). Pang et al., (2013) found grip strength to be the strongest determinant of radius compressive bone strength index (cBSI; a measure of the strength of the bone segment against compressive forces in the distal end of long bones), offering an easy-to-administer assessment to screen stroke patients who may have compromised upper extremity bone health.

The serum concentrations of deoxypyridinoline, intact parathyroid hormone, and the mean serum ionized calcium levels were significantly higher in patients with stroke than that of the control subjects. The mean serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations in patients were significantly lower than those of the control group. Bone mineral density tests of the proximal femurs in patients with paretic limbs were decreased significantly compared with those of the control group.

17.6.3 Treatment of Osteoporosis Post Stroke

A number of therapeutic interventions intended to maintain bone mineral density and reduce the risk of osteoporosis and subsequent risk of hip fracture have been evaluated. These include: bisphosphonates, isofalavone, vitamins B, D and K, sunlight exposure, and physical activity.

Table 17.20 The Treatment of Osteoporosis Post Stroke

<table>
<thead>
<tr>
<th>Author, Year Country</th>
<th>PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sato et al. (1997) Japan 8 (RCT)</td>
<td>84 patients randomized to receive either 1 μg 1- (OH)_3 daily with 300mg elemental calcium or an inactive placebo.</td>
<td>Bone Mineral Density (BMD) on the hemiplegic side decreased significantly less for those receiving treatment compared to 8.9% of the placebo patients (2.4% vs. 8.9%). BMD on the intact side increased by 3.5 in the treated group while decreasing by 6.3% in the placebo group. 4 of the placebo patients suffered a hip fracture compared to none in the treatment group.</td>
<td></td>
</tr>
<tr>
<td>Sato et al. (1998) Japan 5 (RCT)</td>
<td>108 outpatients recovering from a stroke of 2 years duration or less were randomized to receive 45 mg manaquimine-4 (MK-4), a form of vitamin K_2, or to no treatment, daily for 12 months. The results were compared with 35 healthy control patients Bone mineral density (BMD) was assessed in the 2nd metacarpus along</td>
<td>BMD on the hemiplegic side increased by 4.3% in the MK-4 group and decreased by 4.7% in the untreated group, while BMD on the intact side decreased by 0.9% in the MK-4 group and by 2.7% in the untreated group. At baseline, patients of both stroke groups showed vitamin</td>
<td></td>
</tr>
</tbody>
</table>
with serum indicators of bone metabolism. Vitamin K is known to affect bone metabolism.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uebelhart et al. (1999)</td>
<td>Switzerland</td>
<td>5 (RCT)</td>
<td>34 stroke patients with hemiplegia</td>
<td>allocated to receive either 100 IU of salmon calcitonin or placebo by nasal spray for 2 years. Patients were recruited within the first month of stroke and all patients received active rehabilitation + calcium supplementation of 1000 mg. A variety of markers of bone and connective tissue were assessed before and after treatment.</td>
<td>11 subjects, the majority from the calcitonin group, dropped out over the study period. Biochemical markers of bone formation, serum total alkaline phosphatase, osteocalcin and type I procollagen did not vary during the two years of follow-up. No significant differences were reported between the calcitonin-treated and the placebo group for any of the biochemical markers at any time point.</td>
</tr>
<tr>
<td>Sato et al. (1999)</td>
<td>Japan</td>
<td>5 (RCT)</td>
<td>103 patients randomized to be treated with either 600 mg ipriflavone (an isoflavone) daily for 12 months or 1 μg vitamin D3 daily for 12 months or received no drug treatment.</td>
<td>Bone mineral density on the hemiplegic side decreased by 1.4% in the ipriflavone group, 3.8% in the vitamin D3 group, and 5.4% in the control group. After treatment, serum 1,25-dihydroxyvitamin D level increased by 139.9% in the ipriflavone group and by 26% in the vitamin D3 group. Significant decrease in the serum ionized calcium and pyridinoline cross-linked carboxyterminal telopeptide of type I collagen and increases in parathyroid hormone and bone Gla protein were observed in the ipriflavone group, whereas no changes were noted in the other 2 groups.</td>
<td></td>
</tr>
<tr>
<td>Sato et al. 2 (2000)*</td>
<td>Japan</td>
<td>8 (RCT)</td>
<td>98 stroke patients were randomized to receive 400 mg of etidronate (n=49), cyclically for 56 weeks (2 weeks on treatment followed by 12 weeks no treatment) or placebo (n=49). 40 age-matched controls were followed for 56 weeks.</td>
<td>BMD decreased significantly less on the hemiparetic side of patients receiving etidronate (-2.3% vs. –4.8%, p=0.0003) following treatment. The serum profiles of vitamin D, ionized calcium, parathyroid hormone and bone Gla protein levels also improved in the treatment group compared to control.</td>
<td></td>
</tr>
<tr>
<td>Ikai et al. (2001)</td>
<td>Japan</td>
<td>No score</td>
<td>81 post menopausal women with hemiplegia secondary to first stroke received 200 or 400 mg/day of etidronate (n=40) for 2 weeks or to a control condition (n=41). Women were divided into a low ADL group (motor FIM(\leq) 70) and a high ADL group (FIM &gt; 70).</td>
<td>Following a 3-month rehabilitation program, bone mineral densities (BMD) obtained at the lumbar spine and femoral neck was remeasured. There were no differences in BMD changes between the control or treatment conditions in the high ADL group. There was significantly less bone loss on the paretic side of the femoral neck associated with treatment for the low ADL group (-4.0% vs. –9.6%, p&lt;0.05).</td>
<td></td>
</tr>
<tr>
<td>Sato et al. (2003)</td>
<td>Japan</td>
<td>2 (RCT)</td>
<td>258 post-stroke, vitamin D deficient patients were randomized to receive regular sunlight therapy (n=129)</td>
<td>Metacarpal bone mineral density (BMD) was assessed at baseline and at 12 months. BMD</td>
<td></td>
</tr>
</tbody>
</table>
### Japan 6 (RCT)

187 post-stroke women were randomized to receive a daily dose of 2.5 mg risendronate for 12 months, or placebo. The incidence of hip fracture was compared between the two groups.

Seven patients sustained hip fractures on the hemiplegic side in the placebo group, and one hip fracture occurred in the risendronate group. The odds of hip fracture in the control group were 7 times higher. Bone mineral density increased by 1.5% in the risendronate group and decreased by 4.9% in placebo group. Urinary deoxypyridinoline, a bone resorption marker, decreased by 53.4% in the risendronate group and increased by 35.8% in the placebo group.

### Sato et al. (2005)

628 patients with stroke of at least 1 year duration and with high levels of serum homocysteine and low levels of serum folate and cobalamin (vit B12) were randomized to receive 5 mg of folate and 1500 mcgobalamin daily or placebo for 2 years. The incidence of hip fracture was assessed at the end of the study period.

There were significantly fewer hip fractures in the active treatment group compared to placebo (6 vs. 27).

### Sato et al. (2005)

280 post stroke males aged > 65 years were randomized to received risendronate (2.5 mg orally) or placebo for 18 months. The incidence of hip fracture and markers of bone resorption were compared at the end of the study period.

The incidence of hip fracture was lower in the study group (2 vs. 10, relative risk = 0.19; 95% confidence interval, 0.04 - 0.89). Bone mineral density increased by 2.5% in the study group and decreased by 3.5% in the placebo group (P<.001). Urinary deoxypyridinoline, a bone resorption marker, decreased by 58.7% in the risendronate group and by 37.2% in the placebo group.

### Sato et al. (2005)

96 elderly women with post stroke hemiplegia resulting from a stroke sustained at least two years previously were randomized to receive 1,000 IU of ergocalciferol or to placebo for 2 years. Muscle strength tests and histological examinations of muscle tissues were used to assess the effects on skeletal muscle.

Patients in the study group experienced significantly fewer falls over the 2 year period (22 vs. 136), translating to a 59% reduction in falls. There was no incidence of hip fractures among patients in the study group, while there were 4 in the control group. There were increases in the relative number and size of type II muscle fibers and improved muscle strength in the vitamin D-treated group. There were no differences in mean serum ionized calcium or serum parathyroid hormone between the groups.

### Poole et al. (2007)

27 patients with stroke onset of 35 days or less who were unable to ambulate were randomized to receive a single intravenous infusion of 4 mg zoledronate, a bisphosphonate, (n=14) or placebo (n=13). Patients in both groups received calcium and vit. D supplements. Bone mineral density (BMD) was assessed after one year.

Mean total hip BMD was unchanged in the hemiplegic hip of the zoledronate group (mean 0.0% change). The corresponding change in the placebo group was -5.5%, with the greatest bone loss observed in the trochanteric subregion (mean, -8.1%). On the unaffected side the mean change in total hip BMD was +1.0% with zoledronate versus a mean change of -2.7% without. The differences between groups were statistically significant. There were no fractures during the study period. The number of
At baseline, both groups had low BMD with high levels of serum ionized calcium and urinary deoxypyridinoline. In the etidronate group, serum calcium and urinary deoxypyridinoline levels decreased significantly during the study period, whereas the levels in the placebo group were increased. BMD on the hemiplegic side increased by 1.4% in the etidronate group and decreased by 2.2% in the placebo group (P < .001). Two patients sustained hip fractures in the placebo group, and no hip fracture occurred in the etidronate group (p=0.16).

Small effect sizes were detected in favour for PA interventions. Significant differences (P<0.05) were found between intervention and control groups for paretic limb femoral BMD (0.00% (95%CI -0.02 to 0.01) vs. -0.02% (-0.03 to -0.01), mid-tibial cortical thickness at the 50% site (0.4 ± 2.2 vs. -0.9 ± 1.9mm) and 66% site (0.1 ± 0.1 vs. 0.0 ± 0.1mm), and distal tibial trabecular BMC (5.6 ± 6.7 vs. -0.5 ± 10.8mg).

At the end of the trial, there were no statistically significant clinically apparent osteoporotic fracture incidence differences between the treatment and placebo group.

A summary of the results from the table above is presented in Table 17.21.

### Table 17.21. A Summary of the Effectiveness of Pharmacological Treatments For Osteoporosis

<table>
<thead>
<tr>
<th>Author, Year PEDro Score</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sato et al. 1977</td>
<td>Vitamin D + calcium</td>
<td>BMD* + Hip fracture +</td>
</tr>
<tr>
<td>Sato et al. 1998</td>
<td>Vitamin K</td>
<td>BMD + Hip fracture - Changes in urinary/serum markers +</td>
</tr>
<tr>
<td>Uebelhart et al. 1999</td>
<td>Calcitinin</td>
<td>Markers of bone metabolism -</td>
</tr>
<tr>
<td>Sato et al. 1999</td>
<td>Ipriflavone (isoflavone) vs. Vit D₃</td>
<td>BMD + Hip fracture - Changes in urinary/serum markers +</td>
</tr>
<tr>
<td>Sato et al. 1999</td>
<td>Etidronate</td>
<td>BMD + Changes in urinary/serum markers +</td>
</tr>
<tr>
<td>Ikai et al. 2001</td>
<td>Etidronate</td>
<td>BMD -</td>
</tr>
<tr>
<td>Sato et al. 2003</td>
<td>Sunlight</td>
<td>BMD + Hip fracture +</td>
</tr>
<tr>
<td>Sato et al. 2005 a</td>
<td>Risedronate</td>
<td>BMD +</td>
</tr>
</tbody>
</table>
Four distinct mechanisms by which stroke patients may suffer from bone loss (preferentially on their paretic side) following stroke have been identified (Sato et al., 1997). These factors included disuse due to paralysis, vitamin D deficiency, secondary to immobility-induced hypercalcaemia, lack of sunlight and or dietary insufficiency, compensatory hyperparathyroidism and vitamin K deficiency. Vitamin D deficiency has been associated with osteomalacia, which has in turn been associated with an increased risk of hip fracture.

Sato et al. (2001) reported that hemiparetic stroke patients with serum levels indicating a deficiency of vitamin D had a higher incidence of hip fracture compared to patients with insufficient or normal serum vitamin D levels (7 vs. 1 vs. 0). Sato et al. (1997), reported that stroke patients who were treated with 1α-hydroxyvitamin D3 and supplemental calcium experienced significantly less loss of bone mineral density on both the hemiparetic and intact sides relative to patients who were treated with calcium supplement and placebo. No patients treated with vitamin D fractured their hip during the study period compared to four patients in the control group. Treatment with vitamin D stimulates absorption of calcium from the gut and may depress bone turnover. Further research has confirmed the previous findings (Sato et al. 2005). Over a two-year period patients treated daily with vitamin D had a lower incidence of falls and hip fracture (4 vs. 0). Muscular strength and quality of type II muscle fiber was also improved.

Suto et al. (1999) has also evaluated the efficacy of Ipriflavone (a flavanoid compound) and 1α-hydroxyvitamin D3 on preservation of bone mineral density following stroke. The authors reported that Ipriflavone was significantly more effective than vitamin D in preventing bone mineral loss following stroke. Treatment with Ipriflavone appeared to decrease serum calcium levels by inhibiting osteoclastic bone resorption while activating osteoblastic bone formation. The same group of authors recently reported an increase in BMD associated with exposure to sunlight, among a group of vitamin D deficient stroke patients (Sato et al. 2003).

Treatment with bisphosphonates (or diphosphoanates as they are also referred to), including risedronate, etidronate and alendronate appear to be beneficial in reducing bone loss following stroke by inhibiting bone removal by osteoclasts. Risedronate may be advantageous as it is thought to reduce the likelihood of gastro-intestinal side effects compared with the other bisphosphonates. Risedronate is also more potent in blocking the dissolution of bone than etidronate and alendronate. A meta-analysis (Iwamoto et al. 2008), selected, in part, due to the narrow confidence intervals associated with the overall point
estimate, reported a significant 75% reduction in the risk of hip fracture associated with treatment (RR: 0.25, 95% CI 0.13-0.48, p<0.0001) in patients with one of three neurological diseases (stroke, Alzheimer’s disease and Parkinson’s disease). Overall, the treatment effect was greater in men compared with women.

Six studies evaluated the effectiveness of bisphosphonates. All of the trials were positive and reported increased bone mineral density and reduced the incidence of falls. Findings showed that risedronate was effective in both women and men (Sato et al. 2005, 2005). The NNT to prevent one hip fracture was 28 for women and 16 for men. The authors attribute the higher number for women to be explained by other factors such as post-menopausal osteoporosis. Sato et al. (2000) previously conducted a 56-week randomized trial to evaluate the efficacy of intermittent cyclical etidronate therapy in hemiplegic acute stroke patients. Compared to either control patients who received no therapy or patients who received a placebo, patients randomized to the etidronate group experienced significant decreases in serum ionized calcium and significantly less BMD losses on the paretic side. Etidronate appears to prevent decreases in the BMD in hemiplegic stroke patients by decreasing the serum calcium through inhibition of bone resorption and causes a subsequent increase in the serum 1, 25(OH)2D concentration.

Poole et al. (2007) noting that significant bone loss occurs early on following stroke and that many patients are dysphagic, hypothesized that an intravenous bisphosphonate would be an effective means to provide the treatment compared with tablet form. Although treatment was effective in maintaining bone mass, its effect on reducing hip fractures is unknown given the absence of its occurrence in either group.

The Canadian Medical Association (CMA) released its practice guidelines for the diagnosis and management of osteoporosis (Brown & Josse 2002). While the guidelines do not include stroke specific therapies, they may be appropriate or adjunctive, given pre-existing risk factors or evidence of the disease. Pharmacological interventions such as bishosphonates and estrogen therapy (for women) may be considered as treatment options and may help to prevent bone loss following stroke. They have been evaluated and shown to have good efficacy in two of the reviewed studies although one study was not a RCT. Unfortunately, oral bisphosphonates are not well absorbed from the gut and may be inappropriate for patients with dysphagia or for those who have difficulty sitting or standing upright. Intravenous pamidronate also helps reduce bone loss in stroke patients although it has been proven to be beneficial for spinal cord injured patients to date.

Mechanical hip protectors have also been used successfully to reduce the incidence of hip fractures associated with falls, although compliance with these devices can be poor (Kannus et al. 2000). Poole et al. (2002) suggested a combination of hip protectors and intravenous bisphosphonates might afford the best protection against hip fractures among stroke patients.

**Conclusions Regarding the Treatment of Post-Stroke Osteoporosis**

*There is moderate (Level 1b) evidence that vitamins D and K and sunlight therapy reduces osteoporosis in hemiplegic stroke patients.*

*There is also moderate (Level 1b) evidence that Ipiflavone was more effective than vitamin D in reducing osteoporosis in hemiplegic stroke patients.*

*There is also strong (Level 1a) evidence that treatment with bisphosphonates (risedronate and etidronate can preserve bone mineral density following stroke.*
There is moderate (Level 1b) evidence that risedronate and a combination of folate and Vit B 12 can prevent hip fracture in elderly women following stroke.

There is a lack of evidence (more research is needed) for physical activity maintaining or improving bone density and bone structure on the paretic side in chronic stroke patients.

Treatment with Ipriflavone, vitamins D and K, sunlight therapy, and bisphosphonate, reduces the risk of osteoporosis post stroke.

17.7 Central Pain States Post Stroke

About one hundred years ago, a couple French neurologists described an abnormal pain disorder occurring subsequent to stroke (Segatore 1996). Central post stroke pain (CPSP) is a syndrome characterized by sensory disturbances and neuropathic pain. The condition has received a significant amount of attention recently (Andersen et al. 1995; Boivie 1992, 1994; Boivie et al. 1989; Jensen & Lenz 1995; Leijon & Boivie 1989, 1989; Leijon et al. 1989; Vestergaard et al. 1995). One study reported that as many as 8% of all stroke patients had some form of CPSP. However, given the multitude of clinical impairments/disabilities suffered by stroke patients it is not unusual for pain to be ignored or given a lower priority (Jensen & Lenz 1995). In 40-60% of CPSP patients, the onset of central pain occurs more than one month following the stroke and may cause delays in diagnosis and treatment if the primary care providers are no longer actively involved in the patients’ care at this point (Hansson 2004).

17.7.1 The Incidence of Central Pain Post Stroke

Central Post Stroke Pain is generally regarded as rare, occurring in less than 2% of strokes (Mucke & Maciewicz 1987; Pagni 1976; Tasker 1990). Some authors report an incidence as high as 8% among unselected stroke patients, with 5% reporting moderate to severe pain (Andersen et al. 1995) (Andersen et al., 1995) (see Table 17.22). Determining the actual incidence of CPSP is difficult since most studies have been based on selected cases (Hansson 2004). A prolonged gap between the stroke event and the onset of pain may also hinder a diagnosis.

Table 17.22 The Incidence of CPSP

<table>
<thead>
<tr>
<th>Author, Year Country PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Andersen et al. (1995) Denmark No Score</td>
<td>All consecutive patients less than 81 yrs with acute stroke admitted to hospital were examined within 7 days and followed at 1, 6 and 12 months post stroke. CPSP was considered present if the patient complained of pain and if sensibility to touch, temperature and pinprick were abnormal compared to the contralateral areas tested.</td>
<td>267 patients entered the study. 207 patients survived for at least 6 months. CPSP was reported in 16 (8%) patients. 15 patients also demonstrated evoked dysesthesia or allodynia. In patients with a single cerebral lesion there was no association between size or location of the lesion and CPSP. Pain was reported as light in 6 (3%) patients and moderate to severe in 10 (5%).</td>
</tr>
<tr>
<td>Bowsher (2001) UK No Score</td>
<td>Questionnaires about stroke and subsequent pain were administered to 1,071 elderly subjects (median age 80 years, 537 female) by nurses.</td>
<td>Seventy-two patients (6.7%), median age of 74 had completed strokes. At least 8 (11%) of the completed stroke subjects had what seemed to be central post-stroke pain (CPSP). Their median age at the time of the stroke was 77.5 years; all</td>
</tr>
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</table>
Widar et al. (2002)  
Sweden  
No Score  
Of 528 patients who had been admitted to a single hospital within the previous 2 years, those with chronic pain were identified and interviewed about the characteristics of their pain. Pain was assessed using the Pain-O-Meter and a Pain questionnaire.  
185 (37%) patients had died within the 2-year period. 356 patients were excluded due to cognitive impairment or Aphasia. 245 patients did not meet inclusion criteria. 43 patients with long-term pain were identified, 15 of whom were diagnosed with central pain. Median pain intensity was 6/10. 6 patients reported that the pain was continuous. Cold and stress/anxiety were identified as factors contributing to increasing pain.

Jonsson et al. (2006)  
Sweden  
No Score  
297 patients were followed over a one-year period following stroke (population based Lund Stroke Register). Worst pain intensity during the previous 48 hours was assessed on a 0-100 point visual analogue scale (VAS), where 0 to 30 was defined as no or mild pain; 40 to 100 as moderate to severe pain. NIH stroke scale (NIHSS) score was assessed at baseline.  
Moderate to severe pain was reported by 96 patients (32%) after four months (median VAS =60). Predictors of pain were younger age, female sex, greater stroke severity and raised HbA1c at stroke onset. At 16 months, only 62 patients (21%) had moderate to severe pain, but pain intensity was more severe (median VAS score=70; p<0.016). Higher pain intensity correlated with female sex, worse depression, better MMSE score, and raised HbA1c. Pain was persistent in 47%, disturbed sleep in 58%, and required rest for relief in 40% of patients.

Klit et al. (2011)  
Denmark  
No Score  
A questionnaire was sent out to all (n = 964) stroke patients identified through the Danish National Indicator Project Stroke Database, between March 2004 and February 2005. All surviving patients who fulfilled 4 questionnaire criteria for possible CPSP (n = 51) were selected for further clinical examination, and their pain was classified by using stringent and well-defined criteria and a detailed, standardized clinical examination.  
608 questionnaires were completed. 35 (5.8%) patients had definite or probable CPSP and the prevalence of CPSP-like dysesthesia or pain was 1% of the total sample. Pinprick hyperalgesia was present in 57%, cold allodynia in 40%, and brush-evoked dysesthesia in 51% of patients with CPSP.

Conclusions Regarding the Incidence of Central Pain Post Stroke

The incidence of central pain post stroke may be as high as 8% but is generally felt to be much lower.

Central pain states post stroke are uncommon, but not rare.

17.7.2 Pathophysiology of Central Pain Post Stroke

Central pain resulting from a stroke is often referred to as "thalamic pain" despite the fact that in many patients with CPSP, the cerebrovascular lesions do not involve the thalamus (Agnew et al. 1983; Bowsher 1985; Fields & Adams 1974; Garcin & Lapresle 1969; Leijon et al. 1989; Loh et al. 1981). Leijon et al. (1989) noted that central pain states occurred following lower brainstem, thalamic and suprathalamic cerebrovascular events. CPSP is invariably associated with a lesion involving the spinothalamic-cortical pathway with a disturbance in temperature and pain sensation (Andersen et al. 1995).

At present, the pathophysiology of CPSP states remains unknown. It is becoming increasingly clear that damage to the spinothalamiccortical pathway is associated with CPSP (Andersen et al. 1995; Boivie et al. 1989; Dejerine & Roussy 1906; Jensen & Lenz 1995; Vestergaard et al. 1995) although not all patients
with damage to this pathway experience pain (Andersen et al. 1995). CPSP is always associated with impaired sensory perceptions to cold and warm stimuli and to pinprick; these somatosensory functions are mediated by the spinothalamic tract (Boivie 1992; Boivie et al. 1989; Vestergaard et al. 1995). However, touch, 2-point discrimination and vibration sense, generally regarded to be mediated by lemniscal pathways in the CNS and often involved in CPSP states, may be intact (Boivie et al. 1989; Vestergaard et al. 1995). Vestergaard et al. (1995) reported that lemniscal system lesions are not necessary for the development of CPSP.

Most, but not all cases of CPSP, are associated with hyperalgesia and/or allodynia. This paradoxical presence of a sensory deficit in combination with hyperalgesia in that part of the body de-afferented by the stroke lesion suggests a central sensitization of third and fourth order CNS neurons as a result of loss of spino-thalamic (or thalamo-cortical) input (Vestergaard et al. 1995). Hyperexcitability of thalamic or cortical neurons could evoke the perception of pain. Vestergaard et al. (1995) noted that 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 a central hyperexcitability (Bennett & Laird 1992; Dubner 1991; Wall 1991).

Conclusions Regarding the Pathophysiology of Post-Stroke Central Pain

Damage to the spinothalamiocortical tract appears to be necessary with denervation hyperexcitability of cortical or thalamic neurons being the most popular hypothesis for the pain.

Spontaneous or evoked dysesthesia, allodynia/hyperalgesia are manifestations of central post-stroke pain.

17.7.3 Clinical Symptoms of Central Pain Post Stroke

Central pain is often described as a "burning" sensation in association with an unpleasant sensation of tingling, pins and needles, or numbness (Tasker 1990). It often is described in terms such as ripping, tearing, pressing, twisting, aching, pricking, and lacerating (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 an abnormally unpleasant somatosensory experience, often poorly localized, elucidated by normally non-nociceptive stimuli (allodynia) (Andersen et al. 1995). Hyperalgesia is defined as an increased pain response to a normally painful stimulus (Andersen et al. 1995). Leijon et al. (1989) in their study of 23 patients with CPSP secondary to a known cerebrovascular lesion, noted little difference in the character of the pain in relation to the site of the lesion with the exception that "burning" pain was more commonly described with brainstem and suprathalamic lesions while "lacerating" pain was seen more with the thalamic lesions. Andersen et al. (1995) in their study of 16 patients with CPSP noted no relation between size or location of the stroke and the presence of CPSP. The pain normally happens within an area smaller than the sensory impairment and is generally constant and often associated with spontaneous paroxysms of pain (Boivie et al. 1989; Frese et al. 2006; Leijon et al. 1989; Tasker 1990). It also can be exacerbated by physical movement, emotional stress, loud noises or voices, changes in the weather, cold, and light touch (Boivie et al. 1989; Leijon et al. 1989; Tasker 1990).

Virtually all patients with CPSP report spontaneous or evoked parasthesias and/or dysaesthesia (Andersen et al. 1995; Leijon et al. 1989). Spontaneous dysaesthesias occur in the majority of CPSP patients while almost all demonstrate some hypersensitivity to external somatic stimuli (Leijon et al. 1989). Hence, the spontaneous pain seen in central pain states may be accompanied by further
unpleasant effects induced by somatosensory stimuli known as hyperalgesia, allodynia, and dysesthesia. Hypersensitivity to sensory stimuli may make it difficult to initially differentiate from other pain entities, such as reflex sympathetic dystrophy, in the upper extremity. Anderson et al. (1995) noted 9 of 16 CPSP patients (56%) reported allodynia to cold stimulation while another 9 (56%) reported allodynia to touch.

All patients with CPSP generally have some kind of sensory abnormality on the affected side (Boivie et al. 1989). Decreased pinprick and threshold abnormalities to temperature detection are invariably present. However, touch, vibration and 2-point discrimination are more variably involved. Allodynia and hyperalgesia have been discussed. Paralysis is not necessarily a feature of CPSP patients. Ones study found that 52% (14/27) of patients with CPSP were left with no paresis, 37% (10/27) had moderate paresis and only 11% (4/37) had severe paresis (Leijon et al. 1989). The original thalamic pain syndrome described by Dejerine and Roussy (1906) was associated with a thalamic lesion and was characterized by slight hemiplegia, abnormal sensation, hemiataxia and hemiastereognosia, intolerable pain and choreoathetoid movements (Andersen et al. 1995). Thalamic or central pain states post stroke are generally characterized by burning, stabbing, knife-like pains and dysesthesias while allodynia and hyperalgesia are frequently present. The frequencies of sensory abnormalities associated with CPSP are summarized in table 17.23.

CPSP does not necessarily begin immediately after the stroke. Andersen et al. (1995), in their review of 16 CPSP patients, noted 10 (63%) reported pain onset within one month of the stroke, 3 (19%) within 1-6 months, and 3 (19%) after more than 6 months.

**Table 17.23 Sensory Abnormalities Associated with Central Post Stroke Pain (CPSP)**

<table>
<thead>
<tr>
<th>Author, Year Country PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bovie et al. (1989)</strong>&lt;sup&gt;a&lt;/sup&gt; Sweden No score</td>
<td>27 stroke patients with CPSP were evaluated clinically with neurological tests and quantitatively.</td>
<td>All patients demonstrated abnormal temperature and pain sensibility. 25 patients had raised thresholds to thermal pain and 26 had abnormal sensibility to pin prick stimulus. 24 patients demonstrated hyperpathia, 23 somatic stimuli evoked dysesthesia. Paraesthesias were reported in 11 patients, radiation of stimuli in 14, after-sensations in 12 and allodynia in 6.</td>
</tr>
<tr>
<td><strong>Vestergaard et al. (1995)</strong> Denmark No score</td>
<td>The sensory abnormalities in an unselected, consecutive group of 11 stroke patients with CPSP, surviving more than 1 year were examined.</td>
<td>Median present spontaneous pain intensity on a visual analogue scale was 3.3 (range:0-7.7). Warmth detection threshold was higher in the pain area in all patients. 10 patients had an increased cold detection threshold. A cold allodynia in the 10-15 °C range was present in 6 patients.</td>
</tr>
</tbody>
</table>

**Conclusions Regarding the Clinical Presentation of Post Stroke Central Pain**

*Central pain states are seen in brainstem, thalamic and suprathalamic lesions. CPSP reported burning or lacerating pain, generally constant with paroxysms of pain. Spontaneous dysesthesias are seen in the majority of cases, with hyperalgesia and allodynia also frequently present.*
17.7.4 Treatment of Central Pain Post Stroke

“Pain after stroke is a symptom often forgotten, unnoticed although it is reported to be a great problem in care,” (Widar & Ahlstrom 2002). Most neuropathic pain responds poorly to NSAIDS and opioid analgesics. As a result, the mainstay of treatment are predominantly tricyclic antidepressants (TCA’s), anticonvulsants and systemic local anesthetics, antiarrhythmics, opioids, anti-epileptic agents and N-methyl-D-aspartate (NMDA) antagonists. Recently, post-stroke pain has been treated with motor cortex stimulation in various trials for mitigation of neuropathic pain of various aetiologies (Canavero & Bonicalzi 1999; Katayama et al. 1998; Katayama et al. 2001;Nandi et al. 2002; Yamamoto et al. 1997). There are few trials evaluating the efficacy of any of these treatments, which tends to be managed on a symptomatic basis.

Frese et al. (2006) conducted a systematic review of studies investigating pharmacologic treatment of central post-stroke pain. The review included seven small RCTs, six uncontrolled trials and one case series. The study reported that oral drugs effective in treating CPSP were amitriptyline and lamotrigine. Although IV drugs such as lidocaine, propofol and ketamine were effective for short-term control of CPSP, due to possible side effects their application use is inappropriate for long-term treatment. Gabapentin was also reported useful in controlling CPSP for several patients.

A Cochrane review (Wiffen & Rees 2007) assessing the benefits of acute and chronic pain concluded that Lamotrigine was not an effective treatment for post-stroke pain, based on the results from only a single RCT, while Kumar et al. (2009) concluded that amitriptyline and lamotrigine should be considered first-line drugs for CPSP following a recent review of the literature.

Newer antiepileptic medications have been considered as alternatives for management of CPSP including Levetiracetam (Keppra). Jungehulsing et al., (2013) recently studied the use of levetiracetam in patients with CPSP in a placebo controlled, double blinded, crossover RCT involving 42 patients who were randomly assigned to levetiracetam or placebo for 8 weeks followed by a 2-week washout and 8 weeks of the other arm of the study. The study authors concluded that levetiracetam was not effective in the treatment of CPSP as there was no significant benefit over placebo.

Table 17.24 The Treatment of Central Post Stroke Pain

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leijon &amp; Boivie (1989) (b)</td>
<td>Sweden</td>
<td>6 (RCT)</td>
<td>A double-blind, 3 phase crossover placebo controlled trial of 15 patients. Treatment was given in randomized order, for 4 weeks, separated by 1 week wash-out periods in which patients were administered amitriptyline, carbamazepine and placebo.</td>
<td>Amitriptyline produced a significantly greater reduction of pain when compared to placebo at week 4.</td>
</tr>
<tr>
<td>Leijon &amp; Boivie (1989) (c)</td>
<td>Sweden</td>
<td>No Score</td>
<td>15 stroke patients received both high frequency and low frequency transcutaneous electrical nerve stimulation (TENS) 3x/day for 16 days. A 10-step verbal pain rating scale was used for the assessments (baseline, 60 and 120 minutes following stimulation). Final follow-up at 23-30 months.</td>
<td>4 patients obtained at least a 20% reduction in baseline pain (mean=42%). 3 patients continued to use TENS and reported an improvement in their pain symptoms for 23, 24 and 30 months.</td>
</tr>
<tr>
<td>Awerbuch et al. (1990)</td>
<td>9 patients (8/9 with stroke) were administered 150 mg/day of mexiletine for 3 days followed by 300</td>
<td></td>
<td>Mexiletine produced a significant improvement in pain in 8 of the 9 patients.</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Score</td>
<td>Dose</td>
<td>Methodology</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>-------</td>
<td>------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>0</td>
<td>10mg/Kg/day for 3 days and thereafter at a dose of 10mg/Kg/day for one month.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Katayama et al. (1997)</td>
<td>Japan</td>
<td>No Score</td>
<td>20 stroke patients received both naloxone (up to 8 mg) and normal saline in a randomized crossover trial. Visual analogue scale and verbal pain scores were obtained immediately before and after injection. There was a 2 to 3 week washout period.</td>
<td></td>
</tr>
<tr>
<td>Yamamoto et al. (1997)</td>
<td>Japan</td>
<td>No Score</td>
<td>39 central post-stroke patients were tested with the 3 pharmacological tests including the morphine, thiamylal and ketamine. After the tests were completed patients were treated with motor cortex stimulation. Follow-up took place at 12-months since the start of stimulation.</td>
<td></td>
</tr>
<tr>
<td>Attal et al. (1998)</td>
<td>France</td>
<td>No Score</td>
<td>18 patients with peripheral nerve injuries or central lesions (2 CPSP patients) received gabapentin in gradually increasing doses of up to 2400 mg/day for a period of 6 weeks. Doses started at 300 mg 2 times daily for the first 3 days, then the dose increased every 3 days.</td>
<td></td>
</tr>
<tr>
<td>Katayama et al. (1998)</td>
<td>Japan</td>
<td>No Score</td>
<td>31 patients with post stroke pain were treated with motor cortex stimulation delivered through surgically implanted devices which delivered a pulse of 0.2 msec duration, frequency of 25-50 Hz and intensity of 2-8 V. Stimulation was applied for 10-20 min on each occasion.</td>
<td></td>
</tr>
<tr>
<td>Attal et al. (2000)</td>
<td>France</td>
<td>6 (RCT)</td>
<td>16 patients (6 with stroke) received both lidocaine and saline intravenous injections 3 weeks apart in a randomized crossover trial. Patients recorded pain using a visual analogue scale every 15 min up to 120 minutes and again at 6 hours.</td>
<td></td>
</tr>
<tr>
<td>Lefaucheur et al. (2001)</td>
<td>France</td>
<td>5 (RCT)</td>
<td>18 patients (12 stroke) with intractable neurogenic pain of various origins were randomized in a crossover design to receive a single 20 min session of 10 Hz, 0.5 Hz and sham rTMS over the motor cortex. Treatments were separated by 3 weeks. Pain was assessed before and after treatment using a 10-point visual analogue scale.</td>
<td></td>
</tr>
<tr>
<td>Lefaucheur et al. (2001)</td>
<td>France</td>
<td>3 (RCT)</td>
<td>14 patients with intractable pain due to thalamic stroke (n=7) or trigeminal neuropathy (n=7) were randomly assigned, in a crossover design, to receive a single 20-min session of rTMS of the motor cortex at 10 Hz using a 'real' and a 'sham' coil. Treatments were separated by 3 weeks. Pain was assessed using a 0-10 visual analogue scale from day 1 to day 12 following the rTMS sessions.</td>
<td></td>
</tr>
<tr>
<td>Vick &amp; Lamer (2001)</td>
<td>USA</td>
<td>No Score</td>
<td>Case report of a 68-year-old female with CPSP and long standing depression treated with ketamine. Her pain had been refractory to therapy with many agents including opioids, lidocaine, NSAIDS, mexilitine and antidepressants. Following 14 mg of i.v. ketamine, the patients reported marked pain relief and reduced allodynia and hyperalgesia. Oral doses of 50 mg t.i.d were continued. Side effects were effectively managed with diazepam.</td>
<td></td>
</tr>
</tbody>
</table>
| Katayama et al. (2001) | Japan | No Score | 45 patients with post-stroke pain received spinal cord stimulation at higher levels produced more
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Description</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2001) Japan No Score</td>
<td></td>
<td></td>
<td>stimulation (SCS), and if that failed they were considered for deep brain stimulation (DBS) of the ventralis caudalis (VS) and/or motor cortex stimulation (MCS). A visual analog scale was used to evaluate the stimulation therapy.</td>
<td>frequent satisfactory pain control (7% by SCS, 25% by DBS and 48% by MCS). Stimulation by VC, post-central, pre-central and pre-frontal cortices caused some painful sensation, but as the stimulation site was raised to higher levels the sensation was less frequent.</td>
</tr>
<tr>
<td>Vestergaard et al. (2001)</td>
<td>Denmark</td>
<td>8 (RCT)</td>
<td>30 consecutive patients with CPSP from two centers were entered into a double-blind, placebo-controlled cross-over study evaluating lamotrigine. There were two 8-week treatment periods separated by 2 weeks of wash-out. The primary endpoint was the median value of the mean daily pain score during the last week of treatment while treated with 200 mg/d lamotrigine. Secondary endpoints were median pain scores while on lamotrigine 25 mg/d, 50 mg/d, and 100 mg/d; a global pain score; assessment of evoked pain; areas of spontaneous pain; and allodynia/dysesthesia.</td>
<td>Lamotrigine 200 mg/d reduced the median pain score to 5, compared to 7 during placebo (p = 0.01). No significant effect was obtained at lower doses. Twelve patients (44%) responded to the treatment. Lamotrigine only had significant effects on some of the secondary outcome measures. Oral lamotrigine 200 mg daily is a well tolerated and moderately effective treatment for central post-stroke pain.</td>
</tr>
<tr>
<td>Attal et al. (2002) France</td>
<td></td>
<td>8 (RCT)</td>
<td>The efficacy of morphine infusion (9-30 mg) was assessed in a double-blind, placebo-controlled, crossover study of 15 patients with post stroke-6 patients) or spinal cord injury-9 patients) related pain. All of the patients subsequently received sustained oral morphine.</td>
<td>Morphine significantly reduced the intensity of brush-induced allodynia but had no effect on other evoked pains (i.e., static mechanical and thermal allodynia/hyperalgesia). The effects of morphine on ongoing pain were not significantly different from those of the placebo, but 7 patients (46%) responded to morphine. There was a correlation between the effects of morphine on spontaneous pain and the decrease of the responses to suprathreshold thermal stimuli on the nonpainful contralateral side. Only 3 patients (20%) were still taking morphine after 1 year.</td>
</tr>
<tr>
<td>Shimodozono et al. (2002)</td>
<td>Japan</td>
<td>No Score</td>
<td>28 patients with central post-stroke pain received selective serotonin reuptake inhibitor (SSRI) fluvoxamine 50 mg/day divided into 2 weekly doses. Doses were either increased or maintained (maximum of 125 mg/day) depending on the symptoms of the patient with the treatment lasting 2 to 4 weeks. Evaluations took place before and after treatment. They included the visual analog scale (VAS) and Zung's Self-rating Depression Scale (SDS).</td>
<td>Following treatment patients' mean VAS and mean SDS significantly decreased (p&lt;0.01). After, patients were split up into 2 groups, the patients in whom the duration after stroke was less than 1 year post-stroke showed a significant reduction in VAS (p&lt;0.001), whereas patients who had longer than 1-year duration since stroke onset did not.</td>
</tr>
<tr>
<td>Serpell et al. (2002) UK</td>
<td></td>
<td>8 (RCT)</td>
<td>307 patients with a wide range of neuropathic pain syndromes (9 with post stroke pain) with at least two of the following symptoms: allodynia, burning pain, shooting pain, or hyperalgesia were randomized to receive either gabapentin (n=153) or placebo (n=152) for 8-weeks following a run-in period. Gabapentin was given in three divided doses, initially titrated to 900 mg/day over 3 days, followed by two further increases, to a maximum of 2400 mg/day if required by the end of week 5. The primary outcome measure was changed in average daily pain diary score (baseline versus final week) using a 0-10 Likert scale.</td>
<td>Over the 8 week study, pain scores decreased 1.5 (21%) in gabapentin treated patients and by 1.0 (14%) in placebo treated patients (P=0.048, rank-based analysis of covariance). Significant differences were shown in favour of gabapentin for the clinician and patient Global Impression of Change, and some domains of the Short Form-McGill Pain Questionnaire. Improvements were also shown in patient-reported outcomes in quality of life, as seen by significant differences in favour of gabapentin in several domains of the Short-Form-36 Health Survey.</td>
</tr>
</tbody>
</table>
| Lampl et al. (2002)           |             |          | 39 stroke patients were randomly assigned to receive | There were no differences in the occurrence,
<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Study Details</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>7 (RCT)</td>
<td>81 patients</td>
<td>High-strength or low-strength pregabalin</td>
<td>Pain relief; EQ-5D scores; Pain Disability Index scores</td>
</tr>
<tr>
<td>USA</td>
<td>7 (RCT)</td>
<td>33 patients</td>
<td>Ketamine or placebo</td>
<td>Pain relief; VAS scores; SF-36 scores</td>
</tr>
<tr>
<td>France</td>
<td>7 (RCT)</td>
<td>44 patients</td>
<td>Crossover design</td>
<td>Pain relief; VAS scores; SF-36 scores</td>
</tr>
<tr>
<td>France</td>
<td>4 (RCT)</td>
<td>60 right-handed patients</td>
<td>TMS of the motor cortex</td>
<td>Pain relief; VAS scores; SF-36 scores</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>9 (RCT)</td>
<td>40 patients</td>
<td>Pregabalin</td>
<td>Pain relief; EQ-5D scores; Quality of life (SF-36)</td>
</tr>
<tr>
<td>Brazil</td>
<td>No Score</td>
<td>27 patients</td>
<td>Motor cortex stimulation</td>
<td>Pain relief; VAS scores</td>
</tr>
</tbody>
</table>

Mean VAS scores decreases significantly from 7.9 to 3.8 (p<0.001). 15 patients experienced a 50% or more reduction in pain; while in ten patients (38.5%), more than 60% of the original pain was relieved.
**Kim et al. (2011)**  
South Korea  
9 (RCT)  

| Patients with CPSP were randomized to receive either 150-600 mg of pregabalin (n=110) or placebo (n=109) over 13 weeks. The primary endpoint was the mean pain score on the Daily Pain Rating Scale over the last 7 days on study drug up to week 12 or early termination visit. | The mean pain scores were reduced from 6.5 to 4.9 in the pregabalin group and from 6.3 to 5.0 in the placebo group. The difference was not statistically significant. (p=0.578). Treatment with pregabalin resulted in significant improvements, compared with placebo, on secondary endpoints including some aspects of sleep, anxiety (HADS-A), and clinician global impression of change (CGIC) P<0.05. Adverse events were more frequent with pregabalin than with placebo and caused discontinuation in 9 (8.2%) of pregabalin patients versus 4 (3.7%) of placebo patients. |

**Lefaucheur et al. (2011)**  
France  
No Score  

| 6 patients with CPSP resistant for more than 1 year to at least 3 analgesic medications were surgically implanted with an 8-contact lead for motor cortex stimulation. Pain was assessed using a 100 point VAS, the Brief Pain Inventory (BPI)(0-100) and the McGill Pain Questionnaire. Additional assessments included the Sickness Impact Profile and the Patient Global Assessment of Change scale. All assessments were conducted before implantation and at months 1,3,6 and 12. Compared with preoperative baseline, 2 patients were totally relieved of central poststroke pain, 3 patients were very much relieved, and 1 patient remained unchanged at the final examination. |

**Vranken et al. (2011)**  
The Netherlands  
9 (RCT)  

| 48 patients with central pain were randomized to receive escalating doses of either duloxetine (60 and 120mg/day) or matching placebo capsules for 8 weeks. In both groups, patients started with 1 capsule per day. If pain relief was insufficient, patients were titrated to a higher dose. The primary outcome was pain relief assessed using a 10-point VAS. Additional outcomes included Patient Disability Index (PDI), EQ-5D, SF-36 and the Patients Global Impressions of Change (PGIC). A trend towards a decrease in mean pain score after eight weeks was observed for duloxetine treatment (7.2 to 6.1 vs. 7.1 to 5.0 p=0.05. There were no differences between groups in PDI or EQ-5D scores but patients in the duloxetine group reported better pain scores on the bodily pain sub section of the SF-36 (p=0.035). More patients in the duloxetine group considered their situation to have improved based on the PGIC score. |

**Jungehulsing et al. (2013)**  
Germany  
8 (crossover RCT)  

| 42 patients with CPSP of at least 3 months duration and a pain score ≥ 4 on an 11-point Likert scale were treated over two 8-week periods with Levetiracetam (max dose 3000 mg) or placebo. The primary endpoint was a median pain lowering at least 2 points in the final treatment week compared with the last baseline week. Secondary outcome measures included additional pain ratings, depression, sleep quality, quality of life and patients’ global impression of change. 33 patients completed the study. Side effects and withdrawals were more frequent in the treatment group (n = 5 vs. n = 1). At the end of the active treatment period there was no significant improvement in median pain scores between groups or in any of the secondary outcomes. |

Central pain is generally intractable to most therapeutic interventions. Narcotic and non-narcotic analgesics consistently failed to provide adequate pain relief (Nuzzo & Warfield 1985). Tricyclic antidepressants have been shown to have a beneficial effect on central pain states (Koppel 1986; Tourian 1987). In one controlled study (PEDro = 6), amitriptyline was shown to have some pain ameliorating effect on CPSP patients (Leijon & Boivie 1989) (see able 17.13). The authors suggested that the reduction in pain was not attributable to an antidepressive effect. Phenothiazines (chlorpromazine) (Margolis & Gianacol 1956), anticonvulsants [phenytoin (Cantor 1972; Mladinich 1974) and carbamazepine (Leijon & Boivie 1989)] are reportedly only minimally effective in reducing pain (Bowsher Supplementary Table S17.1).
Apo-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 two trials a course of pregabalin treatment was associated with improvement in pain relief scores (Kim et al. 2011; Vranken et al. 2008).

In 4 trials, the efficacy of a single session of rTMS on chronic pain was evaluated. Three of the 4 studies were published by the same group of authors. All of these trials reported significant short-term improvements in pain following a single treatment.

Transcutaneous electrical nerve stimulation was reported to be effective in some CPSP patients (Leijon & Boivie 1989). Sympathetic blockade in the form of stellate ganglion and lumbar sympathetic blocks or local venous guanethidine blocks may provide some temporary relief of pain (Loh et al. 1981). A variety of operative treatments have been tried for central pain states. These include neurosurgical brain lesioning (Davis & Stokes 1966; Mark et al. 1961; Nashold et al. 1969; White & Sweet 1969), brain stimulation (Meyerson 1979; Sweet 1982) and even stereotaxic chemical hypophysectomy (Levin et al. 1983). Overall, neurosurgical ablative procedures have been reported in uncontrolled studies to have a 25% effectiveness rate in permanently relieving central pain states but are associated with a significant risk of brain injury (Pagni 1976). Gonzales (1994) reported that resistance to treatment of CPSP can evoke severe depression, which poses a risk of suicide at this stage (Gonzales 1994).

**Table 17.25 Summary of RCTs Evaluating The Treatment of Central Post-Stroke Pain**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>PEDro Score</th>
<th>N</th>
<th>Intervention</th>
<th>Main Outcome(s) Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. 2011</td>
<td>9 (RCT)</td>
<td>220</td>
<td>Pregabalin vs. placebo</td>
<td>Daily Pain Rating Scale (-)</td>
</tr>
<tr>
<td>Vranken et al. 2011</td>
<td>9 (RCT)</td>
<td>48</td>
<td>Duloxetine vs. placebo</td>
<td>Visual Analog Scale pain (-)</td>
</tr>
<tr>
<td>Vranken et al. 2008</td>
<td>9 (RCT)</td>
<td>40</td>
<td>Pregabalin vs. placebo</td>
<td>Visual Analog Scale pain (+)</td>
</tr>
<tr>
<td>Vranken et al. 2005</td>
<td>9 (RCT)</td>
<td>33</td>
<td>Ketamine vs. placebo</td>
<td>Pain Disability Index (+)</td>
</tr>
<tr>
<td>Andre-Obadia et al. 2006</td>
<td>8</td>
<td>12</td>
<td>rTMS</td>
<td>Pain Disability Index (-)</td>
</tr>
<tr>
<td>Vistergaard et al. 2001</td>
<td>8 (RCT)</td>
<td>30</td>
<td>lamotrigine vs. placebo (8 wk cross-over study)</td>
<td>Median Pain Score (+)</td>
</tr>
<tr>
<td>Attal et al. 2002</td>
<td>8 (RCT)</td>
<td>15</td>
<td>IV morphine vs. saline (2 wk cross-over study)</td>
<td>Visual Analog Scale (-)</td>
</tr>
<tr>
<td>Serpell et al. 2002</td>
<td>8 (RCT)</td>
<td>9</td>
<td>Up to 2400 mg/day of gabapentin vs. placebo</td>
<td>Visual Analog Scale (+)</td>
</tr>
<tr>
<td>Canavero &amp; Bonicalzi 2004</td>
<td>7 (RCT)</td>
<td>44</td>
<td>Propofol vs. placebo</td>
<td>Visual Analog Scale pain (+)</td>
</tr>
<tr>
<td>Laml et al. 2002</td>
<td>7 (RCT)</td>
<td>39</td>
<td>Amitriptyline treatment vs. placebo</td>
<td>Visual Analog Scale (-)</td>
</tr>
<tr>
<td>Rowbotham et al. 2003</td>
<td>7 (RCT)</td>
<td>81 (10 CPSP patients)</td>
<td>High-strength (0.75-mg) vs. low-strength (0.15-mg) capsules of µ-opioid agonist levorphanol</td>
<td>Pain Reduction (+)</td>
</tr>
<tr>
<td>Leijon &amp; Boivie 1989(b)</td>
<td>6 (RCT)</td>
<td>15</td>
<td>Amitriptyline vs. carbamazepine vs. placebo (4 wk cross-over study)</td>
<td>Pain Intensity (+) Comprehensive Psychopathological Rating Scale (-)</td>
</tr>
<tr>
<td>Lefaucheur et al. 2001a</td>
<td>5</td>
<td>18</td>
<td>rTMS</td>
<td>Visual Analog Scale (+)</td>
</tr>
</tbody>
</table>
Conclusions Regarding the Treatment of Post Stroke Central Pain

The majority of cases appear to be largely intractable to treatment.

There is conflicting (Level 4) evidence that treatment with anticonvulsant drugs results in a reduction of pain post stroke.

There is strong (Level 1a) evidence that antidepressant drugs are not effective in reducing central pain.

There is strong (Level 1a) evidence that treatment with intravenous injections of propofol, lidocaine or morphine results in short-term (up to 45 min) pain relief.

There is strong (Level 1a) evidence that rTMS helps reduce the symptoms of post-stroke pain in the short term.

There is moderate (Level 1b) evidence that high-strength μ-opiod agonist levorphanol is effective in reducing pain in post-stroke patients.

The majority of central pain states post stroke do not respond well to treatment although a broad range of drug treatments are available.

17.8 Post–Stroke Fatigue

Although fatigue following stroke is common and may negatively affect progress during inpatient rehabilitation, it has not been well-studied. Fatigue is a subjective term and there is no valid and accepted definition of fatigue (Choi-Kwon & Kim 2011; Van Eijsden et al. 2012). Abnormal, or pathological fatigue has been defined as a state of general tiredness characterised by weariness unrelated to previous exertion levels and is usually not ameliorated by rest (De Groot et al. 2003). Accurate biological correlate of post stroke fatigue are difficult to ascertained (Kutlubaev et al. 2012) due to variable assessment, different study population and study designs.

A review by Choi-Kwon & Kim (2011) stated that the predisposing factors to post stroke fatigue can be classified into 3 main catagories: physiological (functional disability, prestroke fatigue, medical comorbidities, medication, sleep disturbances, and nutritional problems), psychocognitive (depression and cognitive dysfunction), and organic (damage to particular brain areas with consequent neurochemical alterations, perfusion deficit). A variety of risk factors have been identified and include chronic pain, depression, certain medications, sleep disorders, disability level and neurological impairment (Feigin et al. 2012; Hoang et al. 2012; Mead et al. 2011). The variables female sex and age emerged most consistently as independent predictors of fatigue in predictions models. Controversy exists as to whether there is a causal relationship between depression and fatigue.
17.8.1 Incidence of Fatigue

The estimates of post-stroke fatigue vary widely, depending on the measure used to assess it and the timing of assessment, but have been reported to be between 30% to 74% (Table 17.26). There is also evidence that fatigue both increases and decreases in frequency over time following stroke (Duncan et al. 2012).

**Table 17.26 Prevalence of Post-Stroke Fatigue**

<table>
<thead>
<tr>
<th>Author, Year Country PEDro Score</th>
<th>Study Population &amp; Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schepers et al. (2006) The Netherlands No Score</td>
<td>167 patients admitted with first-ever supratentorial stroke for inpatient rehabilitation were included. Fatigue was assessed at admission, 6 months and 1 year. The Fatigue Severity Scale was used. A score of ≥ 4 was considered positive.</td>
<td>At admission, 6 months and 1 year, fatigue was identified in 51.5%, 64.1% and 69.5% of patients.</td>
</tr>
<tr>
<td>Van de Port et al. (2007) The Netherlands No Score</td>
<td>223 patients admitted for inpatient stroke rehabilitation from 4 centres were included. The Fatigue Severity Scale was used. A score of ≥4 was considered positive.</td>
<td>At 6, 12 and 36 months post stroke, fatigue was identified in 68%, 74% and 58% of patients.</td>
</tr>
<tr>
<td>Snaphaan et al. (2011) The Netherlands No Score</td>
<td>108 ischemic stroke patients admitted acutely to a neurology department were screened for fatigue at 2 months and 1.5 years after stroke onset. Fatigue was assessed using the Checklist Individual Strength. A score below 36 was considered positive.</td>
<td>The prevalence of fatigue was 35% and 33%, at 2 months and 1.5 years respectively.</td>
</tr>
<tr>
<td>Christensen et al. (2008) Denmark No Score</td>
<td>165 ischemic or hemorrhagic stroke patients admitted to 3 stroke units were included and a reference group of 1,069 people from the Civil Registration system were included. Fatigue was assessed at 10 days, 3 months, 1 year and 2 years following stroke onset. The Multidimensional Fatigue Inventory was used. Score of ≥12 was considered positive.</td>
<td>At 10 days, 3 months, 1 year and 2 years following stroke onset, fatigue was identified in 59%, 44%, 38% and 40% of the patients respectively. This was considerably higher than that reported in the sample from the general population.</td>
</tr>
<tr>
<td>Feigin et al. (2012) New Zealand No Score</td>
<td>613 ischemic stroke patients from the population-based Auckland Regional Community Stroke study, who were enrolled and followed for 6 months. Fatigue was assessed using the SF-36 Vitality Score</td>
<td>Fatigue was identified in 183 (30%) of patients at 6 months.</td>
</tr>
<tr>
<td>Hoang et al. (2012) France No Score</td>
<td>32 stroke patients recruited from the outpatient department of a rehabilitation hospital were included. Fatigue was assessed using the Fatigue Severity Scale at an average of 40 months following stroke. A score of ≥4 was considered positive.</td>
<td>Fatigue was identified in 11 (66%) patients.</td>
</tr>
<tr>
<td>van Eijdsen et al. (2012) Netherlands No score</td>
<td>250 stroke patients were enrolled and followed up for 24 week. Measurement of fatigue was assessed using the Fatigue Severity Scale (FSS) administered at T0 (baseline) and T1 (24 weeks). Total score ≥4 was classified as fatigue.</td>
<td>Fatigue was reported by 58.3% at T0 (baseline) and 55% at T1 (24 weeks). Mean FSS was 4.1 (SD 1.7) at both measurements.</td>
</tr>
</tbody>
</table>
Naees et al. (2012) Norway No Score 377 stroke patients, at least 6 months post stroke onset responded to postal questionnaire which included Fatigue Severity Scale (FSS), HADS and Barthel Index. 42.3% of responders reported having post stroke fatigue (defined as FSS score ≥5)

Parks et al. (2012) Canada No Score 522 patients in the prospective Stroke Outcome Study (SOS) were enrolled and followed up at 1 year post stroke. 228 of the initial cohort completed follow-up. An interview was performed to determine various aspects of functioning and quality of life at 12 months. Fatigue was assessed using Fatigue Impact Scale (FIS). 36.8% (84/228) participants reported fatigue at least once a month at 12 months post stroke. Younger age at the time of stroke was the only significant predictor of increased fatigue measure at 12 months.

Radman et al. (2012) Switzerland No Score 99 stroke patients with non-disabling stroke [NIHSS <6 in acute, ≤3 after 6 months; mRS score <1 at 6 months] were assessed at acute, 6 months and 12 months. Fatigue was assessed using the Fatigue Severity Scale. Fatigue was reported in 30.5% at 6 months, and 34.7% at 12 months.

Conclusions Regarding the Prevalence of Post-Stroke Fatigue

The prevalence of post stroke fatigue ranges between 30% and 74% of stroke survivors.

17.8.2 Treatment of Post-Stroke Fatigue

Since the etiology of post stroke fatigue is multifactorial and not fully understood the approach to treatment is varied. Pharmacological and non-pharmacological approaches have been investigated.

18.8.2.1 Pharmacological Treatment of Post Stroke Fatigue

A Cochrane review (McGeough et al. 2009) identified two randomized controlled trials, which examined the use of drug therapy (fluoxetine and tirilazad). In the fluoxetine vs placebo trial, there were no differences in mean fatigue scores between groups following treatment Trilazad was more effective than placebo, but the trial was small and inclusion was restricted to women with SAH (Choi-Kwon et al. 2007). The authors concluded that there was insufficient evidence to guide treatment decisions.

In the non-placebo controlled study by Brioschi et al (2009), patients with brainstem or diencephalic stroke showed positive response with modafinil compared to patients with cortical stroke. The authors concluded that fatigue in patients with brainstem-diencephalic strokes may be caused by dysfunctional reticular activating systems and that modafinil, a drug originally used to treat patients with hypersomnia or narcolepsy, benefits only those stroke patients whose lesions involve the reticular system. Unfortunately, the study was not placebo-controlled, and the number of patients was too small to arrive at a conclusion.

Table 17.27 Pharmacological Treatment of Post-Stroke Fatigue

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<tr>
<th>Author, Year Country PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
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Choi-Kwon et al. (2007) Korea 6 (RCT)

83 consecutive outpatients with post stroke fatigue (PSF) at an average of 14 months after the onset of stroke were randomized to receive 20 mg/day of fluoxetine (n = 40) or placebo (n = 43) for 3 months. PSF was assessed at baseline, and 3 and 6 months post stroke using a visual analogue scale (VAS) and Fatigue Severity Score (FSS). The presence of post-stroke depression, post-stroke emotional incontinence and post-stroke anger proneness were also evaluated.

There were no differences in the number of patients with PSF between the fluoxetine group and the placebo group at 3 and 6 months after the treatment. The percent changes in VAS scores and FSS at all follow-up assessments were not significantly different either. Fluoxetine significantly improved post-stroke emotional incontinence (p < 0.05) and post-stroke depression (p = 0.05) in the patients with PSF.

Brioschi et al. (2009) Switzerland No PEDro score

14 brainstem or diencephalic stroke (BDS) patients, 9 cortical stroke (CS) patients and 17 multiple sclerosis (MS) patients were included in this non-placebo controlled study which aimed to compare fatigue observed in different neurological pathologies, to evaluate the tolerability to modafinil, and to describe changes in subjective fatigue. The Fatigue Assessment Instrument severity scale was performed at baseline, after 3 months of modafinil and after 1 month of washout. Cognition, mood and somnolence were assessed. A subgroup of 14 patients underwent activity measures before and during treatment.

Thirty-one patients completed the study (10 BDS, 9 CS, 12 MS). The responder profile is more frequent in MS than in CS (p = 0.04), and in BDS than in CS patients (p = 0.04). Actiwatch measures showed no changes in activity during, before and after therapy. Modafinil was tolerated in 75% of patients at small doses and seemed to improve the severity of fatigue in the MS and BDS groups but not in the CS group.

Conclusions Regarding the Pharmacological Treatment of Post-Stroke Fatigue

There is moderate (Level 1b) evidence that treatment with an antidepressant does not alleviate symptoms of post-stroke fatigue.

There is limited evidence to support modafinil as a treatment for post stroke fatigue in patients with brainstem and diencephalic stroke

18.8.2.2 Non-Pharmacological Treatment of Post Stroke Fatigue (PSF)

Table 17.28 Non-Pharmacological Treatment of Post-Stroke Fatigue

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<th>Author, Year Country PEDro Score</th>
<th>Methods</th>
<th>Outcomes</th>
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<td>Clarke et al. (2012) New Zealand 4 (RCT)</td>
<td>16 individuals 3 to 18 months post incident stroke with PSF were allocated to a Fatigue Management Group (FMG) or General Stroke Education (GSE) control group. The treatment group received 6 psychoeducational sessions (60 minutes each) including sessions on sleep/relaxation, exercise and nutrition, mood and review of fatigue diaries. Patients in the control group also received 6 psychoeducational sessions (60 minutes each) that were not fatigue-focused. Assessments were conducted before and after treatment and at the 3-month follow-up. The primary outcome was the Fatigue Severity Scale.</td>
<td>Both groups had significantly reduced FSS fatigue at the end of follow-up, but the mean FFS score of patients in the FMG was not significantly different than that of patients in the GSE group (5.69 to 4.548 vs. 5.16 to 4.62, p=0.71)</td>
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<td>Zelditz et al. (2012)</td>
<td>This multicenter, assessor blinded, randomized</td>
<td>The qualification period showed stable</td>
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A clinical trial was conducted to compare the effectiveness of combining cognitive therapy (CO) with graded activity training (GRAT), also termed COGRAT, compared to CO only. 83 patients (> 4 months post stroke) were assigned to 12 week of COGRAT or CO-only groups. 73 participants completed treatment, and 68 were available for follow-up. Outcome data were collected at baseline, immediately following treatment, and at 6-month follow up. Primary outcomes were: Checklist Individual Strength–subscale Fatigue (CIS-f) and self-observation list–fatigue (SOL-f)). Secondary outcomes were: Hospital Anxiety and Depression Scale, Stroke-Adapted Sickness Impact Profile, SOL-pain, SOL-sleep-D, 6-minute walk test. Outcome measures. Both treatments showed significant beneficial effects on fatigue (CIS-f: $\eta_p^2=0.48$, $P<0.001$) and other outcomes (except pain and anxiety) with intention-to-treat analyses. Gains for the COGRAT group exceeded those in the CO group with individuals showing clinical improvement on the CIS-f ($\geq 8$ points: 58% versus 24%) and on physical endurance ($\eta_p^2=0.20$, $P<0.001$).

**Conclusions Regarding Non-Pharmacological Treatment of Post-Stroke Fatigue.**

There is moderate *(Level 1b)* evidence that a patient education program does not improve post-stroke fatigue.

There is moderate *(level 1b)* evidence that 12 week cognitive therapy can alleviate persistent fatigue after stroke with better results seen when cognitive therapy is augmented with graded activity training.
17.9 Summary

1. There is moderate (Level 1b) evidence that prompted voiding significantly reduced the number of total incontinent episodes.

2. There is moderate (Level 1b) evidence that biofeedback-assisted pelvic training and behavioral therapy with weekly in-home visits from a nurse practitioner significantly reduces urinary accidents and incontinence.

3. There is moderate (Level 1b) evidence that a functionally oriented rehabilitation approach results in significantly less incontinence than a Bobath conventional approach.

4. There is moderate (Level 1b) evidence that moxibustion can improve urinary tract symptoms.

5. The use of indwelling catheters in stroke patients has not been well studied. However, there is consensus (Level 3) opinion that indwelling catheters should be limited to those patients with intractable urinary retention, skin breakdown, continuous wetness and the need for urinary monitoring.

6. There is moderate (Level 1b) evidence that a nursing evaluation/intervention program can be effective in reducing constipation long-term following stroke.

7. There is moderate (Level 1b) evidence that a morning bowel routine is more effective than an evening bowel routine.

8. The incidence of deep vein thromboembolism (DVT) which is both clinically apparent and silent may be as high as 45% acutely post stroke. This rate may fall to 10% or lower in patients in the sub-acute phase of stroke receiving rehabilitation.

9. There is strong (Level 1a) evidence that anticoagulation significantly reduces the incidence of DVT, compared to placebo. There is strong (Level 1a) evidence that low molecular weight heparin is better than unfractionated heparin in reducing DVTs. There is moderate (Level 1b) evidence that heparin is no better than pneumatic compression in preventing DVTs.

10. There is conflicting (Level 4) evidence that graded compression stockings reduce the risk of proximal DVT.

11. There is conflicting (Level 4) evidence that intermittent pneumatic calf compression devices reduce the risk of the development of DVTs.
12. There is moderate (Level 1b) evidence that thigh-length graded compression stockings reduce the risk of proximal DVT compared with knee-length stockings.

13. The incidence/prevalence of post-stroke seizures varied widely. Ten percent of patients experienced seizure activity within the first two years following stroke.

14. There is no significant difference on the efficacy of any antiepileptic in the management of post stroke seizure. Lamotrigine may be preferred due to relatively less side effects and drug interactions.

15. There is consensus (Level 3) opinion that patients who have experienced seizures post stroke should be given preventative anticonvulsant medication to prevent seizure reoccurrence. No evidence exist for prophylactic measure to prevent early post stroke seizure.

16. There is moderate (Level 1b) evidence that vitamins D and K and sunlight therapy reduces osteoporosis in hemiplegic stroke patients. There is also moderate (Level 1b) evidence that Ipiflavone was more effective than vitamin D in reducing osteoporosis in hemiplegic stroke patients. There is strong (Level 1a) evidence that treatment with bisphosphonates (risedronate and etidronate can preserve bone mineral density following stroke. There is moderate (Level 1b) evidence that risedronate, and a combination of folate and vitamin B 12, can prevent hip fracture in elderly women following stroke.

17. Central post-stroke pain (CPSP) states are uncommon following stroke. Central pain states are seen in brainstem, thalamic and suprathalamic lesions. CPSP reported burning or lacerating pain, generally constants with paroxysms of pain. Spontaneous dysesthesias are seen in the majority of cases, with hyperalgesia and allodynia also frequently present.

18. There is conflicting (Level 4) evidence that treatment with anticonvulsant drugs results in a reduction of pain post stroke.

19. There is strong (Level 1a) evidence that antidepressant drugs are not effective in reducing central pain.

20. There is strong (Level 1a) evidence that treatment with intravenous injections of propofol, lidocaine or morphine results in short-term (up to 45 min) pain relief.

21. There is strong (Level 1a) evidence that rTMS helps reduce the symptoms of post-stroke pain in the short term.

22. There is moderate (Level 1b) evidence that high-strength μ-opiod agonist levorphanol is effective in reducing pain in post-stroke patients.
23. There is moderate (Level 1b) evidence that treatment with an antidepressant does not alleviate symptoms of post-stroke fatigue.

24. There is limited evidence to support modafinil as a treatment for post stroke fatigue in patients with brainstem and diencephalic stroke.There is moderate (Level 1b) evidence that a patient education program does not improve post-stroke fatigue.

25. There is moderate (Level 1b) evidence that 12 week cognitive therapy can alleviate persistent fatigue after stroke with better results seen when cognitive therapy is augmented with graded activity training.
References


