Spinal cord injury
— medium- and long-term management

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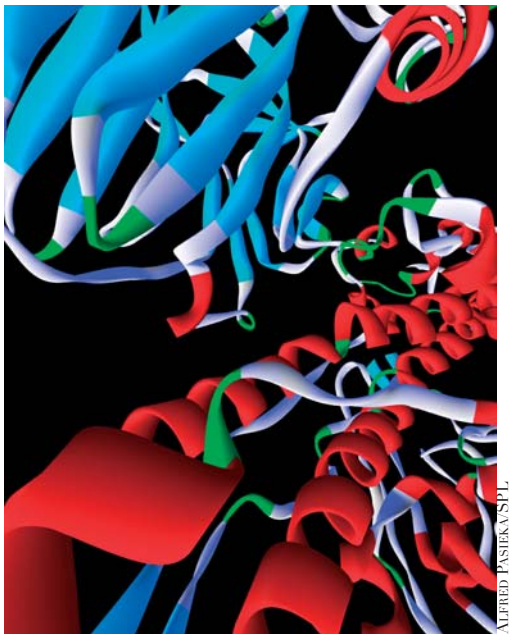
Various physical and psychological problems are encountered by patients with spinal cord injury over the medium and long term. The second part of this month's special feature looks at how some of these issues can be managed, focusing on areas where drug therapy plays an important role



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Computer-generated diagram of botulinim toxin, which is among the agents used to relieve spasticity

Once the acute phase of managing spinal cord injury has passed, subsequent management of the condition consists of a period of rehabilitation that extends to and beyond the patient being discharged from the unit into the community.[1] The period over which this takes place is variable, and can range from a few months to several years.

The major aim of rehabilitation of the patient with spinal cord injury is to maximise the control a patient has over his or her life. Achieving this presents a challenge to health care professionals at least as equal as sustaining life and organ function during the acute phase of the condition. Many problems stem from the fact that a patient is often discharged to his or her home, which can be remote from the specialist spinal unit. Pharmacists can be instrumental in anticipating and addressing medicines management issues that are likely to be encountered by a patient once he or she returns to their community.

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Some complications of spinal cord injury may have arisen during the acute phase, but will require ongoing drug treatment. Examples of these include the need for long-term anticoagulation for immobile patients, who have a chronic risk of thromboembolic disease, and the recognition and prompt treatment of autonomic dysreflexia in patients with high lesions, both of which have been described in our previous article.[2] Other problems assume a greater significance with time and these are set out below.

Skin care

Patients with spinal cord injury are prone to a range of skin conditions, some of which may become serious problems if allowed to develop. In common with other conditions which produce immobility, spinal cord injury can lead to the development of pressure sores which in turn can become infected.[3] The risk is greatest when pressure to soft tissue exceeding capillary pressure is maintained for significant periods to any area of the body. Shear, the term given to displacement of soft tissue relative to the underlying bone, can distort blood vessels and lead to tissue breakdown. Patients with spinal cord injury are particularly prone to pressure sores around the sacral area (ie, lower back). Management rests largely with preventive nursing such as controlling patient movement and the use of pressure mattresses. However, when pressure sores become established, particularly in the sacral area, surgical debridement often becomes necessary.[4]

Bladder management

The nerves controlling the bladder are located at the base of the spinal cord, and so a spinal cord injury at any level will always cause a change in bladder function.

Repeated urinary tract infections and increase in bladder pressure will have a detrimental effect on a patient's kidneys, leading eventually to renal failure if bladder function is not managed appropriately. Renal failure has previously been a major cause of death in patients with spinal cord injury. Modern management, however, incorporating improved techniques of bladder care has reduced renal complications.

The nervous control of normal bladder function is complex but can be simply outlined as follows:

- During normal function as the bladder fills, the sensory nerves within its walls become stretched and send reflex impulses to the spinal cord

- The spinal cord stimulates contraction of the detrusor muscle and so expels urine from the bladder — an action known as the micturition reflex. This occurs at the sacral level (S2–4) of the spinal cord, which is at approximately the same level as the bones of T11-12 (the lower thoracic bones)
- At the same time, impulses are normally conveyed to the brain, which enhance awareness of the need to pass urine. The brain can suppress the micturition reflex until the time and place is appropriate to pass urine. Thus the bladder is normally controlled by the reflex interaction of the sensory and motor nerves

There are two main classifications of bladder dysfunction following spinal cord injury: those in which the micturition reflex is intact ("reflex bladder") and those where it is absent ("acontractile bladder"). In patients with incomplete lesions, or in those with more than one lesion, a combination of these problems may exist ("mixed bladders"). Further details about these are set out in Panel 1.

Catheterisation of a patient will be necessary following spinal injury and may need to be continued indefinitely. It may be possible in time to change to intermittent catheterisation where the patient is only catheterised every four to six hours to drain the bladder. Long-term management may include surgical intervention. Annual surveillance of the urinary tract may detect subclinical problems and allow modification of the bladder regimen before significant complications occur.

The drug management of bladder function varies depending on the level of injury and also on a patient's response.

Anticholinergic drugs Anticholinergic drugs (eg, oxybutynin, tolterodine and probanthine) are the main class of agents used to reduce bladder tone in the hyper reflexic bladder. These drugs act by diminishing unstable detrusor contractions. This allows an increase in bladder capacity, a reduction in urgency and frequency of micturition, a reduction in incontinence and a reduction in bladder pressures. Side effects of the anticholinergic drugs are likely to include dry mouth, which can be relieved with an artificial saliva spray. Other anticholinergic side effects are less common and tend to be dose-dependent.

Different anticholinergic drugs have different side effects and effectiveness. Clinicians may therefore want to try an alternative drug to the one they start treatment with, but it is not rational to use these agents in combination. Using sustained release oxybutynin and tolterodine may reduce side effects in some patients.[5]

An unlicensed preparation of oxybutynin bladder installation is available for patients to self-administer, or for carers to administer to patients. This seems to have greatly improved independence and hence quality of life in many patients with hyper reflexic bladder.[6] Less drug is absorbed systemically when it is administered in this way, and so patients do not suffer as many systemic side effects. It is imperative that patients (or carers) are highly motivated. Maintaining good hygiene and aseptic methods can reduce the risk of serious urinary tract infection. Patients generally have no sensation of pain in the bladder or urethra, so they must be trained carefully to detect any sign of cystitis, and take prompt antibiotic treatment if necessary. Details about how this product is used are set out in Panel 2 (above).

Alpha-1 adrenoceptor blockers Alpha-1 adrenoceptor blockers (eg, tamsulosin, alfuzosin) may be used where there is detrusor sphincter dyssynergia.[7] This condition is basically a loss of co-ordination between the detrusor muscle and the bladder neck, resulting in both these structures contracting at the same time. This leads to pressure build up in the bladder and urine reflux in the ureters, causing damage to the kidneys. Alpha-1 adrenoceptor blockers relax the bladder neck, allowing urine to drain out.

Antibiotics Urinary tract infections occur frequently in spinal injury patients because of repeated catheterisation and incomplete voiding, and so frequent antibiotic courses may be necessary. This includes, in some instances, prophylactic courses.

High dose ascorbic acid High dose ascorbic acid (2–4g daily) is used to produce urine acidification. This reduces the incidence of urinary tract infections and also decreases the incidence of stone and debris formation (which may lead to catheter blockage within the bladder).

Bladder washouts Bladder washouts with antimicrobial agents such as chlorhexidine may also be used to reduce the likelihood of microbial colonisation.

Panel 1: Descriptions of "reflex bladder", "acontractile bladder" and "mixed bladders"

- **Reflex bladder** Reflex bladder occurs when a patient's injury is at a high-level (ie, above T12). The nerves supplying the bladder are still intact but the control from the brain is destroyed. This means that the micturition reflex will still function, resulting in involuntary voiding of the bladder
- **Acontractile bladder** Also known as flaccid bladder, acontractile bladder occurs if a patient has a low-level injury (ie, below T12). There will be no sensation of filling and the bladder will fill until it overflows with a constant dribbling incontinence. The bladder will not empty completely and so is prone to urinary infection. Also, although the pressure in the bladder is not usually high, it can be sufficient to cause kidney damage in the long term if it continually overfills
- **Mixed bladders** Where the spinal lesion is incomplete, there may be a confusing mixture of reflex and acontractile bladder behaviour, with or without sensation. It may appear that the bladder is functioning normally but this may be misleading and careful assessment is required to prevent damage occurring

Panel 2: Intravesicular oxybutynin for self-catheterising patients

- The patient (or carer) inserts a catheter into the urethra and passes it into the neck of the bladder, using strict aseptic technique
- The product containing 5mg oxybutynin in 30ml is introduced through the catheter into the bladder via a syringe
- The catheter is removed, and the drug is maintained *in situ* for several hours, and causes retention of bladder contents during this time
- Another catheter is introduced, and the bladder is emptied
- More oxybutynin solution is introduced

Bowel care

Following spinal cord injury, loss of bowel control is one of the most distressing problems a patient faces. The aim of bowel management is to achieve continence and convenience while preserving a healthy bowel.[8] During rehabilitation a bowel management programme will be established for a patient appropriate to their level of injury. It is important that a patient's regular bowel regimen is followed because constipation can lead to increased spasms or autonomic dysreflexia. A recent National Patient Safety Agency bulletin highlighted this, advising

health care staff not to change established bowel routines and medication regimens.

Laxative use plays an important role in bowel management. A combination of agents may be used. A typical regimen may include senna taken in the evening before planned bowel evacuation the following morning. Senna stimulates stool movement towards the rectum. Applying an irritant to the anorectal area (eg, using a bisacodyl suppository or rectal solution) causes local contraction of the rectum within a short time and allows a patient to pass a motion. This can be repeated daily, or every other day, depending on a patient's needs. Where the stool is too hard to pass because of prolonged colonic transit time, taking additional fibre (eg, Fybogel or in the diet) and fluid (in the diet) may help. However, it should be borne in mind that patients with a lower spinal lesion may experience greater continence with a stool that is firmer, because their anal sphincter might be lax, resulting in incontinence. In other words each patient must be assessed individually and their bowels managed accordingly. Bowel emptying can be a lengthy process and the timing and frequency with which it is done will depend on a patient's clinical requirements and lifestyle. In some patients laxative use may not be necessary as dietary modifications can be sufficient to maintain a healthy bowel.

Spasms

Spasms are involuntary contractions of the paralysed muscle below the level of spinal cord injury caused by reflex activity in the spinal cord. Reflex actions are the involuntary movements triggered from the spinal cord only and are not subject to conscious control. An example would be the response which makes a person automatically pull their hand away from a hot surface. The action relies on the reflex arc, which in this example takes the sensory impulse from the hand to the spine and back to the muscles to move the hand away from danger.

Immediately following the spinal cord injury and during the period of spinal shock there is no reflex function below the level of the lesion and there will be a period of flaccidity. As spinal shock subsides, reflexes return, resulting in spontaneous contractions that cause muscle twitching and movement which, in the early stage, can be mistaken for voluntary movement. Because neuroconnection between the brain and spinal segments below the injury is disrupted, the patient has no control over these movements.

The muscle contractions that occur during spasm help maintain muscle bulk. The muscles can become more toned and more resistant to movement, which is known as spasticity. This may either cause flexion spasms that would, for example, make the elbows and knees bend, or they can cause extensor spasms where the limbs extend and become rigid.

Spasm and spasticity can affect a person's ability to perform everyday tasks such as dressing and eating. They can also become painful. A patient will learn the trigger factors that can initiate a spasm and take measures to avoid them. Interventions to reduce spasms and spasticity rely mostly on the elimination of exacerbating factors and regular muscle stretching through physiotherapy.

Noxious stimuli likely to induce spasms include a blocked catheter, urinary tract stones, pressure sores, constipation and ingrowing toenails. A sudden increase in spasms should be investigated and the stimulus treated if possible.

Spasms, however, can be viewed positively in that they help prevent deep vein thrombosis. They also enable patients to shift their weight, and so can prevent pressure sores. Patients may also learn to trigger spasms to help with transfers into and out of a wheelchair.

Drug therapy for spasms therefore aims at controlling, but not eliminating, them. The drugs used include baclofen, dantrolene and tizanidine, and benzodiazepines (usually diazepam).[9] In managing spasms and

spasticity a single drug, or a combination of two or more agents, may be required. Titration of dosing to optimise the benefits while limiting the side effects may take some time. Ideally, this will usually be achieved before the patient is discharged. However modifications to drug therapy are likely over time. Spasticity tends to be most troublesome during the early years after the injury has happened and with time will become more controllable. Further details about the drugs used are set out below.

Baclofen Baclofen, a gamma aminobutyric acid (GABA) analogue is a centrally acting skeletal muscle relaxant. It inhibits the firing of alpha- and gamma-motorneurones by reducing the release of excitatory transmitters in the spinal cord. It may also act at sites above the spine (ie, supraspinal) by depressing the central nervous system. It is this action that can lead to its side effect of drowsiness, which is dose-dependent and can limit treatment. Patients taking baclofen may also find that they lose too much muscle tone and become too flaccid if excess doses are given.[10] Other side effects include nausea, insomnia, mood changes and altered taste.

Side effects can be minimised by starting at a low dose (5–15mg daily) and gradually increasing according to response (ie, dose titration). The licensed maximum dose is 100mg daily but, within spinal units, higher doses are routinely used where the side effects permit. Baclofen is generally given in four equal doses throughout the day, although larger night-time doses may be given to reduce painful nocturnal spasms. Serious side effects (ie, seizures and hallucinations) can occur if baclofen is withdrawn abruptly. To minimise the risk of these, doses should be gradually withdrawn over two to three weeks.

Intrathecal baclofen Baclofen can be delivered directly into the subarachnoid space using an intrathecal catheter. This produces a greater and constant concentration of baclofen in the cerebrospinal fluid than can be achieved from using the maximum tolerable oral dose.[11]

Intrathecal baclofen is used for patients with severe chronic spasticity who fail to respond to, or are intolerant of, oral antispasticity drugs. Only around 8 per cent of patients with spinal cord injury will fall into this category. Following test doses to ensure that the patient will respond to this form of treatment, an implantable pump is inserted into a patient's abdominal or chest wall, with a catheter placed to deliver the drug direct to the cerebrospinal fluid. A sterile baclofen solution is then introduced into the pump receiver through the pump's filling port.

The type of pump that is used initially will be programmable, with the rate of administration of a fixed concentration of baclofen solution adjusted to meet an individual patient's requirements and the pump's settings being adjusted by telemetry. Because the pumps are battery operated, they have a life span of around five years, after which time they need to be surgically replaced. Once a patient's daily baclofen requirement is established, it may be possible to change to an alternative type of pump, where a factory-set rate of solution is delivered, dose individualisation being achieved by altering the concentration of the baclofen solution. The use of intrathecal baclofen requires meticulous pre-operative assessment, dose titration and post-operative pump management and so can only be undertaken by staff at a specialist centre.

Licensed baclofen intrathecal injection is available at a concentration of 2,000µg/ml. Many centres, however, use higher concentrations (eg, 3,000 to 6,000µg/ml), made by specials manufacturers, so that patients do not need their pumps refilled as frequently. This can reduce the risk of problems, such as the contamination of, and the degradation of, the pump's filling port from multiple needle punctures. It can also reduce the number of times patients need to transfer to the specialist unit, which may be many miles

from their home. An intrathecal dose of baclofen varies from 150 to 800µg or more per day.

Dantrolene Dantrolene acts directly on muscle cells, inhibiting intracellular calcium release and depressing the cells' excitation-contraction coupling.[12]

Doses usually start at 25mg daily and are increased slowly up to a maximum dose for an adult of 100mg four times a day. Muscle weakness is the commonest side effect and drowsiness, dizziness, general malaise and diarrhoea can also occur. Dantrolene is contraindicated in liver impairment. This is because liver dysfunction can occur in 0.7–1 per cent of patients taking dantrolene over a long period, with higher incidences in patients over 30 years and in females, especially those also taking oestrogens. Liver function tests should therefore be performed before and during treatment. Treatment with dantrolene should be stopped if no benefit is seen with adequate doses after four to six weeks or if liver function tests give abnormal results.

Tizanidine Tizanidine is a centrally acting alpha-2 adrenoreceptor agonist. It reduces muscle spasticity by increasing the presynaptic inhibition of motor neurones.[13] The usual starting dose is 2mg daily, increased gradually in 2mg increments according to the clinical response, up to a maximum of 36mg daily. A typical daily dose would be 16–24mg daily in three or four divided doses. The commonest side effects are drowsiness, dry mouth and muscle weakness, although these seem to be less troublesome than with the other anti-spasm medicines. Drug-induced hepatitis is rare but liver function should be checked before the drug is used and at monthly intervals for the first four months of treatment. Checks for other serious side effects, such as hallucinations, should also be made.

Benzodiazepines Benzodiazepines act by facilitating GABA neurotransmissions in the spinal cord at various supraspinal levels, and thereby causing muscle relaxation. Diazepam is the benzodiazepine most commonly used for spasticity at a dose of 5–40mg daily. Tolerance can occur necessitating a higher maintenance dose and presenting withdrawal problems. The anti-spasticity effects of diazepam last longer than its sedative action so the drug is best taken as a single bedtime dose although patients may still feel drowsy in the morning, which can limit its usefulness.

Botulinum toxin Both botulinum toxin type A and B have been used for treating focal spasticity (eg, flexor spasticity resulting from over active biceps) accompanying spinal cord injury.[14] However, the product licences for the available agents vary and they do not all currently cover this indication. When injected into the muscle, botulinum toxin produces muscle weakness that lasts up to three months. This can relieve spasms, improve a patient's posture, function and movements and enable physical treatments to be carried out.

Pain

Pain is common following spinal cord injury, and can be usefully divided into musculoskeletal or neuropathic pain. Brief details comparing these types of pain are set out in Panel 3. A considerably more in-depth review on the pathology and classification of pain arising from spinal cord injury is available elsewhere.[15]

Paracetamol and non-steroidal anti-inflammatory drugs Paracetamol remains the safest analgesic to use in the medium to long term in most patients. Many patients, however, will require more potent pain relief and respond best to an NSAID. Many choices of drug exist, with ibuprofen and diclofenac being suitable for many patients. All NSAIDs carry a risk of gastrotoxicity and it may be wise to give protection (eg, with a proton pump inhibitor), particularly if use is likely to be long-term. Particular concern about NSAID use exists for patients also taking warfarin for the prevention of DVTs. NSAIDS can also cause renal impairment, so a patient's plasma urea and creatinine levels should be monitored regularly, and the drug discontinued if there are signs of nephrotoxicity. In addition to their role in symptom relief, NSAIDS offer some protection against abnormal bone growth (known as heterotopic ossification). This complication of spinal cord injury can otherwise require treatment with bisphosphonates (which are expensive) or surgery to correct.[16]

Opioids Opioids may sometimes be necessary for pain relief. These should be used with caution, particularly in patients with cervical lesions because they may compromise respiratory function. Tramadol (which enhances serotonergic and adrenergic pathways, as well as having an opioid effect) causes less respiratory depression than traditional opioids, although it is occasionally associated with episodes of hallucinations and confusion. All opioids will exacerbate constipation in spinal patients, and their use must always be linked with appropriate bowel management.

Nefopam Nefopam is a centrally acting non-opioid analgesic which is useful in some patients who are non-responsive to, or intolerant of, opioids. It has stimulant effects and should be avoided in patients at risk of convulsions.

Gabapentin Gabapentin has become the most useful drug for many patients with neuropathic pain following spinal cord injury.[17] This agent was originally developed as an anticonvulsant and is structurally related to GABA. Initially, it was considered to function as a GABA analogue, but it is now believed to act primarily by influencing calcium transport in neurones. It has been shown to be effective in divided doses of between 900mg and 2g daily.[18]

Other drugs Other drugs, including fluoxetine and venlafaxine (SSRIs), amitriptyline, lamotrigine, topiramate, valproate and carbamazepine, have been used to manage neuropathic pain in spinal injury with varying success. In addition to their use in managing spasms, benzodiazepines are useful in treating neuropathic pain, with clonazepam being frequently used at doses of up to 1mg four times a day.

Other medication issues

As well as issues specifically relating to their lesions, patients with spinal cord injury can have similar health problems to those of the

Panel 3: A comparison of musculoskeletal and neuropathic pain in patients with spinal cord injury

Musculoskeletal pain

- Results from damage to joints and tissues around the site of the lesion or at other locations that were also subject to trauma during the original trauma that led to the spinal cord injury
- Generally responds to conventional analgesics (eg, paracetamol or opioids), non-steroidal anti-inflammatory drugs or both

Neuropathic pain

- Can occur at any location and, paradoxically, may be present where the patient has no sensation. In this regard it may be considered analogous to "phantom limb pain" in patients with amputated limbs
- Can be an aching and constant pain, or intense and stabbing or burning
- Is resistant to the more typical analgesia used to treat musculoskeletal pain (see above) and requires atypical analgesia

general population. Their disability can, however, have implications as to how they manage these problems. For example, some patients may have diabetes or asthma and modifications to treatment regimens may be necessary in the light of a patient's reduced capacity for managing injections or inhalers. Pharmacists can make a useful contribution in helping patients with spinal cord injuries manage such conditions.

In addition, patients with spinal cord injury are predominantly young, and for many the issue of re-establishing a physical relationship with partners will need to be addressed. Male patients are likely to have erectile dysfunction (partial or total, depending on the location of their lesion) and this may respond to standard treatments such as sildenafil[19] or apomorphine.[20]

When discharged from the spinal injuries unit, a patient may experience particular difficulties with some special medicines that he or she is using. A patient's local hospital or community pharmacy may now be the site where the patient collects his or her other regular medicines, and pharmacists working in these environments may be unfamiliar with some items. Pharmacists linked to spinal units should liaise in advance with a patient's local community pharmacy to prevent problems arising. Information and support available from a variety of organisations and their websites (see Panel 4 above) might also be useful for patients and health professionals.

Conclusion

Spinal cord injury is typically a devastating result of sudden trauma in an otherwise fit and healthy individual. After the patient's condition has been stabilised, and organ function retained, the patient and family undertake a period of rehabilitation which may last several months, during which time ongoing problems are managed. Drug therapy, in addition to other treatments, plays an important role in the medium- and long-term care of patients with spinal cord injury and improves a patient's quality of life.

Proposed spinal cord injury pharmacist network

The authors of this article are seeking to set up an informal network of spinal injury pharmacists to share best practice and to inform others of research or audit work taking place in their unit.

Any pharmacist who is currently working with spinal injuries, has an interest in this area or would be interested in joining this network, should contact Kathy Nichols at Southport and Ormskirk Hospital NHS Trust by e-mailing **Kathy.Nichols@southportandormskirk.nhs.uk**

Panel 4: Useful spinal cord injury organisations and websites

- **Multidisciplinary Association of Spinal Cord Injury Professionals** (MASCIP) provides a national professional forum to promote standards in clinical practice, foster research and encourage the development of health and social care services for people with spinal cord injuries. Visit **www.mascip.co.uk**
- **Spinal Injury Association** is a patient support group for those with spinal cord injury, and for their family and friends. Visit **www.spinal.co.uk**
- **British Association of Spinal Cord Injury Specialists** (BASCIS) works to improve the quality of care for spinal cord injury patients. Although focused on doctors, information useful to all health professionals working in this field is available from their website. Visit **www.bascis.pwp.blueyonder.co.uk**

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