MJD FOUNDATION

MEDICAL PROTOCOLS

Pain, Muscle Cramps, Spasticity & Tremor

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Table of Contents

1. Background – Pain, Spasticity, & Tremor in MJD

The most commonly reported symptom of the neurodegenerative disease Machado Joseph disease (MJD) is impaired mobility (experienced by 80.3% of MJD patients, Schmitz-Hubsch et al., 2010). Nevertheless, other symptoms such as pain, spasticity and tremor are also frequently reported by MJD patients and cause patients a large amount of inconvenience, discomfort and disability. Below we discuss these symptoms and their prevalence, assessment and treatment.

1.1 Pain

Pain is described as an unpleasant sensory and emotional experience in response to noxious stimuli, tissue injury and illness (Handy et al., 2011). Pain can be acute or chronic depending on its duration; acute pain typically lasting only moments, weeks or months whilst chronic pain persists after an injury heals (Grichnik and Ferrante, 1991).

There are many ways to classify pain, including classification based on the aetiology of the pain. Pain may be of *nociceptive origin* if it is a normal response to noxious stimulation or injury (e.g. following skin or musculoskeletal injury), *neuropathic origin* if it is caused by a lesion or disease of the sensory nervous system (e.g. phantom limb pain, diabetic neuropathy) or of *inflammatory origin* when inflammatory mediators such as cytokines activate and sensitize the pain pathways (e.g. appendicitis and rheumatoid arthritis) (Goetz et al., 1986).

Pain is a common symptom of MJD. Franca et al. (2007) study of 70 patients found that 47% of MJD patients were affected by chronic pain, with 41% of patients reporting daily pain, and 33% describing continuous pain. Likewise, Schmitz-Hubsch et al. (2010) reported that the lives of 49.4% of the MJD patients in their study were affected by pain and discomfort.

The mechanism of the pathogenesis of pain in MJD patients is not fully understood. However, Franca et al. (2007) found that chronic pain was correlated with longer CAG repeat lengths in MJD patients. It is currently hypothesised that there are two, often concurrent, mechanisms leading to development of pain in MJD: the occurrence of musculoskeletal pain due to muscle cramps, abnormal postures and gait due to the motor impairment produced by the disease with 80% of MJD patients reporting pain in the lower half of the body, particularly the lumbar region (Franca et al., 2007; Goetz et al., 1986), as well as the occurrence of neuropathic pain due to neurodegeneration of the sensory nervous system pathways (Goetz et al., 1986). It is perceivable that both of these mechanisms would be affected by CAG repeat length. The sensitisation and amplification of painful stimulation produced by neuropathic processes, in addition to the presence of painful stimuli such as cutaneous rubbing and awkward limb positioning, would lead to the ongoing pain that so many MJD patients describe.

1.2 Spasticity, dystonia and muscle cramps

Spasticity and dystonia are two forms of neurological dysfunction that cause muscle stiffness that can be both debilitating and painful. Spasticity is characterised by muscles with high tone (tight, contracted feeling) that makes movement of arms and legs very difficult. Spastic muscles resist the stretch that occurs during movement and this resistance is velocity dependent

(greater resistance when movement of the limb is fast) (Mukherjee and Chakravarty, 2010). Dystonia causes prolonged muscle contractions resulting in uncontrollable twitching and repetitive movements and causes twisted, abnormal postures (Albanese et al., 2013). Both spasticity and dystonia can be described as focal (in one muscle or muscle region), segmental (muscles controlled by nerves from the same spinal cord segment) or generalised (Munchau et al., 1999).

Spasticity and dystonia are common in patients with MJD/SCA3 (found in 44% and 23% MJD patients, respectively) (Jardim et al., 2001; Schmitz-Hubsch et al., 2008). It has also been found that spasticity and dystonia are most common in MJD patients that experienced early disease onset or have a long CAG repeat length (Jardim et al., 2001; Schmitz-Hubsch et al., 2008). Diagnosing and treating the symptoms of spasticity and dystonia in MJD patients is important because it is a symptom that greatly affects the lives of patients. Schmitz-Hubsch et al. (2010) found that dystonia in particular is linked with lower health related quality of life (EQ-VAS scores).

Muscle cramps also involve contraction of muscles in an involuntary manner. In the general population, muscle cramps are usually harmless, lasting only a few minutes. The cause of these harmless muscle cramps is usually muscle fatigue or electrolyte imbalance (Bergeron, 2008). Muscle cramps of a more pathological nature (more frequent, prolonged, debilitating and painful) are a phenomenon often associated with disorders involving lower motor neuron dysfunction (Layzer, 1994; McGee, 1990). Kanai et al. (2003) reported that 80% of the twenty MJD patients within their study experienced pathological muscle cramps. These cramps were frequent (an average of 13 per month) and in 50% of the studied patients muscle cramps disturbed their daily activity and sleep. Muscle cramps were most commonly reported within the legs, trunk and arms of patients.

1.3 Tremor

A tremor is an involuntary, somewhat rhythmic, muscle contraction and relaxation that causes movements (oscillations or twitching) of one or more body part. As MJD primarily effects the cerebellum (posterior region of the brain) patients experience cerebellar tremor, a slow tremor of the extremities that occurs at the end of a purposeful movement (*intention tremor*) caused by damage to the cerebellum (NINDS, 2012). This type of tremor is often most prominent when the person is active or is maintaining a particular posture and produces a combination of rest, action, and postural tremors (NINDS, 2012). Tremor is not a frequent complaint of MJD patients, with reported prevalence rates below 10% (Bonnet et al., 2012) with resting tremor occurring in only 3.6% of MJD patients (Schmitz-Hubsch et al., 2008). Of patients reporting tremor, the most common form of tremor reported is a slow (3-4Hz) resting tremor, but other forms of tremor reported include a faster (6.5-8Hz) frequency tremor occurring in postural/orthostatic situations, (cerebellar) intention tremor and parkinsonian phenotypes (Bonnet et al., 2012; Schmitz-Hubsch et al., 2008).

1.4 Cultural Influences on Pain & Pain Management

Appropriate pain relief for patients in pain, particularly within palliative care settings, is extremely important for patient wellbeing (Wells et al., 2008). In 2000 the Australian National Health and Medical Research Council (NHMRC) identified that the pain experiences of Aboriginal and Torres Strait Islander people, and the best strategies for their management, had not been well studied and were not well understood (Council, 1999). McGrath (2006) has since reported the results of an interview study investigating the issues associated with pain management for Aboriginal people. This study included the interview of seventy-two participants including patients, carers and health care professionals. The study identified key issues including cultural concerns about the reporting of pain and management of pain, and fear of the treatment of pain by Western medicine.

McGrath (2006) and Honeyman and Jacobs (1996) both found within their studies that Aboriginal people do not commonly complain about their pain. Fenwick and Stevens (2004) report that Aboriginal people often believe that pain is caused by the breaking of traditions or violating taboos, and thus Aboriginal people may be ashamed to report pain. This raises the importance of carers being perceptive about the experience of pain in Aboriginal patients, perhaps through the use of pain assessment scales such as the Disability Distress Assessment Tool (see 2.1.1).

Some Aboriginal patients have a fear of pain management using Western medicine. This involves a fear of the sleepiness that is a side effect of many pain medications, concerns about constipation, which some Aboriginal patients fear will produce cultural issues relating to toileting, a fear of becoming addicted to the medications and a fear that the pain management, particularly morphine, may lead to euthanasia (McGrath, 2006; Sullivan et al., 2003). McGrath (2006) found that Aboriginal caregivers may be hesitant to administer pain management medications to their Aboriginal relatives, particularly at end-of-life, for fear of 'blame' or 'payback' in the case of the patient's death. This is of particular concern to Aboriginal people because the end-of-life, particularly for Elders or community leaders, is a significant time for the passing on of traditional knowledge. For this reason, it may be preferred for non-relative health care professionals to manage the end-of-life pain of Aboriginal patients.

Blackwell (1998) points out that many Aboriginal people are afraid of syringes because this is something not used within their traditional medicine practise, and is usually only associated with the care of very sick patients. In her study she recommends the use of transdermal (skin patch) delivery of pain medications instead. Responses within the interviews reported in McGrath (2006) also indicated that many Aboriginal patients would like their health care providers to respect their use of bush medicine to treat their pain.

2. Assessment of Pain, Spasticity, & Tremor in MJD

A thorough assessment of a patient's pain, particularly at first presentation, is important to limit the patient's discomfort and to prevent the progression of the pain from acute to chronic. Important components of the pain assessment include identification of the site of pain, pain intensity, any factors that aggravate or decrease the pain and comorbidities. These details will aid the effective treatment of the underlying cause of the pain and associated comorbidities and effective pain relief.

2.1 Tools Used to Assess Pain

The source of pain is often characterised as being of musculoskeletal, dystonic, neuropathic, mixed or unknown origin (Goetz et al., 1986).

2.1.1 Scales for scoring pain

Pain is often graded using a numerical scale that ranges from 0 to 10 with 0 indicating 'No pain' and 10 indicating 'Worst pain ever' **(Appendix A)**. The average pain score of MJD patients on the visual analogue scale within Franca et al. (2007) was 6.1.

In patients that are non-verbal or having difficulties communicating, for example patients in the later stages of MJD, a Visual Analogue Scale that allows patients to point to the part of the scale that corresponds to their pain intensity can be useful. Further, in adults that have difficulty with the numbers on a numerical scale a facial expression scale such as the Wong Baker Face Scale, which uses faces depicting the levels of pain in addition to corresponding numbers and words, may be needed **(Appendix A)** (Wong and Baker, 1988).

The Disability Distress Assessment Tool (DisDAT) is an additional tool that can be used to assess levels of pain in patients with communication difficulties (Regnard et al., 2007). This assessment tool involves carers completing a questionnaire to document the cues that the patient provides when he/she is content and distressed. This tool is particularly important because it has been found that there is no evidence to indicate that patients have specific signs or behaviours to indicate the presence of pain, but that carers are good at detecting changes in levels of distress, providing a useful guide for making treatment decisions (Regnard et al., 2007).

2.2 Tools Used to Assess Spasticity, Dystonia and Muscle cramps

2.2.1 Scales for Scoring Spasticity, Dystonia and Muscle cramps

Spasticity

The experience of muscle cramps, spasms and dystonia can be assessed clinically through patient questionnaires regarding the intensity, frequency, duration and site of cramps/spasms.

The Ashworth scale was published in 1964 to assist assessment of spasticity in multiple sclerosis patients. In 1987 the scale was modified and renamed the Modified Ashworth scale **(Appendix B)** and was recommended for use for assessing spasticity in to a range of neuronal conditions (Bohannon and Smith, 1987). The Modified Ashworth scale contains six grades of spasticity, numerically ranging from 0-4 (there is 1 and 1+). It involves classification of the amount of resistance present during passive movement of a joint (see Appendix B) (Bohannon and Smith, 1987).

Muscle cramps

In their study Kanai et al (2003) used a 'cramp disability score' to evaluate the extent of disability produced by muscle cramping. The level of disability was graded as:

0- No cramp
1- Mild complaint but no disability
2- Moderate, a chief complaint, sometimes disturbs work/sleep
3- Severe, a chief complaint, disturbs work/sleep daily

They considered muscle cramp to be pathological if the cramps occur more than twice a month.

Dystonia

There are three dystonia grading scales recommended by the Movement Disorders Society for the grading of dystonias relevant to MJD. The Fahn-Marsden Dystonia Rating Scale is recommended for the grading of generalised dystonia and Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) is recommended for the grading of cervical dystonia (Albanese et al., 2013). The Fahn-Marsden Dystonia Rating Scale (FMDRS) is a 120-point scale comprised of a movement subscale, based on patient examination, and a disability subscale, based on the patient's report of disability (Burke et al., 1985). The Unified Dystonia Rating Scale (UDRS) **(Appendix C)** was developed to address the perceived limitations of the FMDRS by dividing the body regions into smaller more defined areas and eliminating the weighting factors and added a new modifying rating scale used for the TWSTRS (Comella et al., 2003).

The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) is the most commonly used scale for assessing cervical dystonia. It is composed of three subscales that score symptom severity, disability, and pain (Consky and Lang, 1994). The severity score is graded by the clinician and the disability and pain scores are graded by the patient. A total score out of 87 is calculated, with higher scores indicating more severe dystonia.

2.2.2 Measuring muscle cramps, spasticity and dystonia

The occurrence of muscle cramps, spasms and dystonia can be monitored objectively through electrophysiological studies. For example, non-invasive nerve conduction studies can be conducted to measure the muscles response to nerve activation. In most cases the nerve is activated via stimulation from electrodes placed above the skin. Measuring the axonal excitability (through measuring the threshold of current required to produce a defined action potential size) has also been used to assess patients with various neurological disorders (Huynh and Kiernan, 2015). Electromyography (EMG) can also be performed to measure electrical activity directly within muscles, through the use of a needle inserted into the muscle to detect local electrical signals. Many believe that EMG is a more sensitive way to detect spasticity than scales such as the Modified Ashworth Scale (Albani et al., 2010). In clinical/neurological practice cramps, spasticity and dystonia are clinically evaluated. The use of EMG or electrophysiological measures is done for research or academic purposes.

2.3 Tools Used for Assessing Tremor

2.3.1 Scales for Scoring Tremor

In 2013 the Movement Disorder Society established a task force to review grading scales for the assessment of tremor (Elble et al., 2013). They reported that the best rating scales for the assessment of tremor severity are the:

-Fahn-Tolosa-Marin Tremor Rating Scale
-Bain and Findley Clinical Tremor Rating Scale
-Bain and Findley Spirography Scale
-Washington Heights-Inwood Genetic Study of Essential Tremor Rating Scale, and
-Tremor Research Group Essential Tremor Rating Assessment Scale **(Appendix D)**

They also reported that the best tremor disability scale is the Bain and Findley Tremor ADL Scale and the best quality of life scale is the Quality of Life in Essential Tremor Questionnaire.

2.3.2 Measurement of Tremor

Objective detection and measurement of tremor can be performed using polymyographic recordings. The use of polymyographic recording allows characterisation of the tremor as either fast (6.5-8Hz) or slow (3-4Hz). Fast tremor has been found to be more common in the earlier stages of the disease, with slow tremor developing at later stages of the disease (Bonnet et al., 2012).

3. Treatments

Few clinical trials have been performed to test the effectiveness of treatments for pain, spasticity, cramp, dystonia or tremor specifically in MJD patients. However, there are a range of treatments, including prescription and non-prescription pharmaceuticals and alternative therapies, that have been examined for the treatment of these symptoms experienced by the general population or patients with other neurological disorders such as spinal cord injury and Parkinson's disease.

The following treatment suggestions are a guide only and the individual circumstances of the patient must be considered.

3.1 Prescription pharmaceuticals

3.1.1 Pain

Most pain experienced by MJD patients is of nociceptive/musculoskeletal origin, caused by injury, strain or irritation of muscles and skin or of neuropathic origin (Franca et al., 2007). The most common pharmaceutical treatments used by the general public for the treatment of mild musculoskeletal pain include medications containing paracetamol (acetaminophen) or the NSAIDS Aspirin or ibuprofen. In more severe pain, addition of the opioid codeine is often suggested. However, the relief provided by opioid analgesic medications is modest and short term (Abdel Shaheed et al., 2016)

In addition to musculoskeletal and dystonic pain, many MJD patients also experience neuropathic pain which would amplify the perception of painful stimuli (Franca et al., 2007). For this reason, consideration of the recommendations for the treatment of neuropathic pain is important when developing a pain management plan for a MJD patient.

In 2007 a Neuropathic Pain Special Interest Group within the International Association for the Study of Pain prepared consensus guidelines for the pharmacological management of neuropathic pain (Dworkin et al., 2007) which were then reviewed and updated in 2010 (Dworkin et al., 2010). These recommendations included the importance of careful diagnosis of neuropathic pain and treating the underlying cause of the pain (e.g. removing irritant or treating disease), as well as detailing a stepwise process to identify the best medication, or combination of medications, to relieve the patient's pain. The recommended stepwise process is shown in **Appendix F**. The guidelines suggest that if a tested medication fails to relieve pain adequately, or causes unacceptable side effects, the medication should be stopped and an alternative medication tested. If a tested medication provides partial pain relief and doesn't cause unacceptable side effects than that medication should be continued and an additional medication that acts via a different pathway can be tested in combination (Dworkin et al., 2010). The classes of medication recommended in the consensus guidelines include first line medications (antidepressants, calcium channel blockers, topical lidocaine), second line medications appropriate for first line treatment in some cases (opioid analgesics and tramadol), and third line medications (certain antidepressant medications, e.g., bupropion, citalopram, and paroxetine, certain antiepileptic medications, e.g., carbamazepine, lamotrigine, oxcarbazepine,

topiramate, and valproic acid, topical low-concentration capsaicin, dextromethorphan, memantine, and mexiletine) (Dworkin et al., 2010). The guidelines state that if none of these classes of medications provide relief than referral to a specialist pain service and/or nonpharmacological treatments may need to be tested.

The full list of pharmacologic treatment options per the NHS NICE guidelines (2014) is listed in **Table 1.** NICE recommends that the following medications only be prescribed by a specialist or with specialist consultation: cannabis sativa extract, capsaicin patch, lacosamide, lamotrigine, levetiracetam, morphine, oxcarbazepine, topiramate, tramadol (referring to long-term use), and venlafaxine.

Table 1. Pharmacological treatments for neuropathic pain

Drug class: subclass	**Drug**	
Antidepressants: tricyclic antidepressants (TCAs)	Amitriptyline Clomipramine Dosulepin (dothiepin) Doxepin	Imipramine Lofepramine Nortriptyline Trimipramine
Antidepressants: selective serotonin reuptake inhibitors (SSRIs)	Citalopram Escitalopram Fluoxetine	Paroxetine Sertraline
Antidepressants: others	Duloxetine Mirtazapine Reboxetine	Trazodone Venlafaxine
Antiepileptics (anticonvulsants)	Carbamazepine Gabapentin Lacosamide Lamotrigine Levetiracetam	Oxcarbazepine Phenytoin Pregabalin Valproate Topiramate
Opioid analgesics	Buprenorphine Co-codamol Co-dydramol Dihydrocodeine Fentanyl	Morphine Oxycodone Oxycodone with naloxone Tapentadol Tramadol
Other treatments	Cannabis sativa extract Flecainide 5-HT1-receptor agonists	Topical capsaicin Topical lidocaine

Antidepressants have been shown to be useful for the treatment of pain due to their action on neurotransmitter levels as well as through the effect of improved mood decreasing the perception of pain. Trials have found that both tricyclic antidepressants (TCA) and serotonin reuptake inhibitors (SRI) are effective in treating several types of neuropathy (Finnerup et al., 2005). Further, the IASP guidelines recommend the testing of secondary amine TCAs for neuropathic pain (Dworkin et al., 2010).

Side effects must be monitored when treating a patient with antidepressants. The most commonly reported side effects include dry mouth, orthostatic hypotension, constipation and urinary retention, which may be symptoms that are amplified in MJD patients. Use of secondary TCAs (e.g. mortriptyline and desipramine) may produce less of those side effects. The selective

selective norepinephrine reuptake inhibitors (SNRI) diltiazem, venlafaxine and milnacipram have also been shown to be effective in treating neuropathic pain.

The anticonvulsant class of drugs have also been reported to reduce neuropathic pain. In their one subject case study, Lo et al. (2011) reported that anticonvulsant gabapentin (taken orally as 400mg every 8 hours, increasing to 500mg every 6 hours) resulted in a decrease in pain experienced by a MJD patient from 8 on the VAS, down to 4, representing a large decrease in perceived pain.

Intrathecal delivery of medications

An alternative to delivering medications orally is to administer the medications directly into the intrathecal space of the spine using a surgically implanted pump with attached catheter inserted into the intrathecal space. The pump can continuously deliver medications, such as those listed above, directly into the intrathecal space allowing lower dosages to be delivered. The need for lower medication dosages decreases the potential and severity of side effects. Nevertheless, this therapy has obvious risks due to the neurosurgical procedure required to implant the pump and catheter. Overdose of the administered medication has also been reported.

Botulinum neurotoxin injection

Botulinum neurotoxin (BTX), derived from the bacterium *Clostridium botulinum,* has been shown to be effective for the treatment of various forms of focal dystonia, spasticity and pain. Several double-blind, placebo-controlled trials have reported that BTX has pain relief effects for certain forms of neuropathic pain, including diabetic neuropathy, complex pain syndrome, trigeminal neuralgia (face pain) and post-traumatic neuralgia (Jardim et al., 2001; McGrath, 2006; Wells et al., 2008; Xiao et al., 2010). Whilst the mechanism of BTX mediated pain-relief is not completely understood, it is thought that it may be related to decreased release of nociceptive neuropeptides at sites of pain (Jardim et al., 2001).

There are currently no guidelines for the appropriate dosage and mode of administration of BTX for neuropathic pain (Jardim et al., 2001). The most common mode of administration found in reported trials is intradermal or subcutaneous injection directly into painful regions. Effective doses sited in the literature vary greatly, but include total doses of 50-200 units, delivered as multiple injections of 4-5 units per injection (Jardim et al., 2001; Wells et al., 2008; Xiao et al., 2010).

When administered by a trained professional BTX is generally considered to be safe and is frequently used as a cosmetic treatment for wrinkles. Nevertheless, cases of irreversible adverse effects have occasionally occurred (Fenwick and Stevens, 2004). Severe overdose of the BTX toxin can cause a potential fatal disease called botulism; for that reason even cosmetic use of BTX must be accompanied by a warning of the potential adverse effects of BTX treatment. Less serious side effects of BTX treatment include reactions at the injection site including infection, pain, bruising and muscle weakness (Council, 1999; Honeyman and Jacobs, 1996).

3.1.2 Spasticity, muscle cramps and dystonia

Botulinum neurotoxin injection

Clinical trials have demonstrated that BTX injection can be an effective treatment for some forms of focal dystonia and spasticity (Blackwell, 1998). The mechanism of BTX injection relief of muscle spasticity and dystonia is through its inhibition of the release of the neurotransmitter acetylcholine, resulting in decreased activity of muscle fibres (Sullivan et al., 2003).
The Food and Drug Administration agency of the United States of America has approved BTX injection for the treatment of blepharospasm (closure of the eyelid), hemifacial spasm (muscle contractions to one side of the face), focal dystonia and upper limb spasticity (Blackwell, 1998). The FDA approved dosage of BTX (Product name Dysport) for the treatment of upper limb spasticity or cervical is 500 units injected into the affected muscle (Truong et al., 2005). The relief provided by BTX lasts an average of 18.5 weeks (Truong et al., 2005).

As with injection of BTX for pain relief purposes, BTX injection for the treatment of spasticity and focal dystonia is not without risks or potential for side effects, as discussed above. Specifically, dysphagia (difficulty with swallowing) and excess weakness are the most common side effects of BTX for spasticity and dystonia (Reviewed in Blackwell, 1998).

Calcium channel blockers

Calcium channel blockers such as diltiazem (30mg) have been reported to decrease the number of muscle cramps experienced, compared to placebo (Voon and Sheu, 2001). Further, within a 9 month trial of 30 patients, the calcium channel blocker gabapentin decreased the frequency of muscle cramps (Serrao et al., 2000).

Other medications

Muscle cramps have been reported to be relieved in MJD patients by treatment with mexilene or carbamazepine (Franca et al., 2007; Kanai et al., 2003). Kanai et al. (2003) reported that mexiletine (oral mexiletine chloride, an analogue of lidocaine, 150mg daily for one month then increased to 300mg daily) produced a marked decrease in the frequency of muscle cramps (mean frequency of three per month down from 24 per month).

A report by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology has recommended the use of Naftidrofuryl (300mg, twice daily, Young and Connolly, 1993), diltiazem (30mg, Voon and Sheu, 2001) or lidocaine injected directly into the muscle (Prateepavanich et al., 1999) for the treatment of muscle cramps (Katzberg et al., 2010)

The subcommittee also reported that although baclofen, carbamazepine and oxcarbazepine are often used for the treatment of muscle cramps their effectiveness for muscle cramps has not be evaluated by clinical trials (Katzberg, Khan and So, 2010). Further, in 2003 Monte et al. reported

the results of a open-label trial that found that fluoxetine, a serotonin reuptake inhibitor, was not effective at improving motor dysfunction in MJD patients (Monte et al., 2003).

Baclofen, however, is a commonly prescribed anti-spastic agent which is widely researched as producing statistically significant improvements in spasticity (Bavikatte & Gaber, 2009).

Levodopa

Levodopa (or L-DOPA) is a dopamine precursor found naturally within the brain that has been harnessed for the treatment of Parkinson's disease. Once administered, L-DOPA is able to cross the blood brain barrier and increase dopamine concentrations within the brain, in turn aiding functions that require dopamine (which is depleted by neurodegeneration of the substantia nigra that produces dopamine). It has been found that in addition to Parkinson's disease L-DOPA can be effective at alleviating some forms of dystonia (called dopamine responsive dystonia), tremor and stiffness. Nunes et al. (2015) reported that although levodopa did not significantly decrease the dystonia of all treated MJD patients within their study, 21% of treated patients did exhibit objective improvements in their dystonia.

L-DOPA delivered alone produces a range of side effects because of it has effects within the peripheral nervous system, in addition to the central nervous system. The side effects include nausea, sleepiness, dizziness and headache (Tarsy, 2014). To prevent these side effects L-DOPA is frequently administered in combination with Carbidopa (a peripheral DOPA decarboxylase inhibitor, DDCI, which prevents its effects on the peripheral nervous system). The combination of L-DOPA and Carbidopa is called Sinemet (composed of 100mg levodopa and 25mg carbidopa) and is given at dosages of one tablet three times a day. Additional side effects are thought to result from troughs in delivery of the levodopa due to its short plasma half-life. For this reason, formulations have been developed that contain entacapone in addition to levodopa and carbidopa (formulation called Stalevo), increasing the plasma half-life and bioavailability (Brooks, 2008). Buhmann et al. (2003) have published one case study of a MJD patient that responded well to L-DOPA/benserazide (750mg/day) with amantadine, tolcapone, entacapone and cabergoline.

3.1.3 Tremor

Levodopa

As described above, L-DOPA treatment is indicated for the treatment of tremor. Bonnet et al. (2012) report that in some MJD patients treatment with levodopa (300-600mg daily) can produce complete removal of tremor. For this reason it has been recommended that L-DOPA should be trialled on MJD patients troubled by tremor.

Anticholinergic medications

When L-DOPA is not successful at treating tremor anticholinergic medications such as benzhexol (Artane, 2-5mg twice daily) or benztropine (Cogentin, 0.5-6mg daily, given as an injection,

starting dose below 2mg daily) should be trialled (Tarsy, 2014). Unfortunately anticholinergic drugs often produce a range of side effects including dry mouth, blurred vision, constipation and urinary retention, dental cavities, memory impairment, hallucinations, and sedation (Lieberman, 2004).

Other medications

Other medications that may aid the treatment of tremor include the dopamine agonists pergolide (Permax), bromocriptine (Somatuline), pramipexole and ropinirole, as well as the antiviral agent (mechanism unknown) amantadine (Symmetrel). The beta-adrenergic blocker propranolol (80-320mg daily) or the anticonvulsant primidone (25-750mg daily) are commonly used for the treatment of essential tremor (Koller and Royse, 1986), and have been found to be particularly beneficial for the treatment of fast tremor, similar to that found in the early stages of MJD. Postural/orthostatic tremor has been found to respond to treatment with the benzodiazepine clonazepam (0.5-2.0mg daily).

3.2 Non-prescription pharmaceuticals

3.2.2 Pain

Over the counter pain medications

The most commonly used non-prescription medications for the treatment of pain are over-the-counter pain relief medications such as those containing paracetamol. Medications containing paracetamol are frequently the first used by patients experiencing pain, particularly musculoskeletal pain. Similarly, the NSAID medications ibuprofen or Aspirin are frequently used for minor pain complaints and are often recommended for pain of inflammatory origin.

3.2.3 Spasticity, dystonia and muscle cramps

Quinine derivatives

The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology has advised that although quinine derivatives (currently approved for the treatment of malaria) are likely effective for the treatment of muscle cramps, they do not recommend their routine use for the treatment of muscle spasms because of potentially severe adverse reactions (Katzberg, Khan and So, 2010). In fact they note there have been 665 reports of serious adverse effects, including 93 deaths. The subcommittee did note that quinine derivatives (e.g. tonic water or Indian tonic water) may be used in patients after special consideration of the risk-benefit relationship (Katzberg et al., 2010).

Vitamin Supplements

A study of 28 patients experiencing muscle cramps showed that treatment with vitamin B complex (including 30mg vitamin B6 daily) resulted in decreased severity of muscle cramps in 86% of patients (Chan et al., 1998). It was noted that this effect was not related to rectifying a vitamin B deficiency.

Short-term vitamin E therapy has also been reported to reduce muscle cramp attacks. A study of 19 patients on haemodialysis administered 400 units daily for 12 weeks reported muscle cramp reduction by 68.3% with no encountered adverse effects (El-Hennawy & Zaib, 2010).

There are various preparations of vitamin B complex, vitamin E, and/or magnesium (see below) marketed for relief if muscle cramps.

Chelated magnesium

Clients of the MJD Foundation have been anecdotally reporting that taking 1-2 chelated magnesium tablet/s per day (up to 1,000mg per day) reduces muscle cramping and spasms, and aids their mobility and balance. However, a subcommittee of the American Academy of Neurology has advised that there is no reported evidence of magnesium preparations being effective for the treatment of muscle cramps (Katzberg, Khan and So, 2010). One trial concluded that while magnesium was not effective for the treatment of nocturnal leg cramps, there may be a real placebo effect – all patients regardless of treatment (magnesium or placebo) improved over time (Frusso et al., 1999).

3.2.4 Tremor

No non-prescription pharmaceuticals are cited in the literature for the treatment of tremor. However, the US National Institute of Health recommends that people experiencing essential tremor avoid caffeine within their diet and get enough sleep (Cleveland Clinic, 2014). However, the effect of caffeine on essential tremor is a contentious issue. In 1987 Koller et al. reported that whilst 8% of patients studied with essential tremor and 6% of patients with Parkinson's disease reported that drinking coffee worsened their tremor, they could not find evidence of increased tremor following caffeine in these patients when tested (Koller et al., 1987).

It is also known that certain medications worsen tremors and avoiding these medications may be considered in some cases of severely disruptive tremor. Medications known to worsen tremor include lithium, valproic acid, corticosteroids, adrenergic agonists and some antidepressants and anti-psychotics (Johns Hopkins Medicine, n.d.) The potential risk of stopping use of those medications should be considered before making any changes to a patient's medication.

3.3 Other treatment strategies

3.3.1 Pain

Physiotherapy, exercise and balance programs

Regular physical activity is commonly recommended to the general population for its benefits for cardiovascular health and general wellbeing. Multiple studies have studied the benefits of physical therapy and exercise programs for spinocerebellar ataxia patients and reported benefits including decreased falls, gait adaptability and even improved SARA scores (D'Abreu et al., 2010; Fonteyn et al., 2014; Santos de Oliveira et al., 2015).

Studies have not yet specifically explored whether physiotherapy and exercise can prevent the development of pain in MJD patients. However, the most common form of pain in MJD patients is musculoskeletal pain in lumbar and lower limb regions and it is postulated that a large contribution to the development of pain in these regions is the abnormal postures and gait that develop due to the disease itself. Studies using physical activity as a therapy for MJD (including programs specifically tailored to improve balance and strength), spinal cord injury, motor neuron disease and Parkinson's disease have found that exercise and balance programs can slow down the decline of a patients balance and gait (Santos de Oliveira et al., 2015). Therefore, it could be hypothesised that physiotherapy and physical activity may delay the development of the abnormal postures and gaits that contribute to the development of this musculoskeletal pain.

Monitoring physical therapy in MJD patients is important to ensure suitable postures and movements are used to prevent injury or additional pain. Further, it should be remembered that MJD patients may fatigue quickly during exercise, so realistic programs should be adopted.

Aids, Orthoses and Equipment

Various pieces of equipment, including braces, casts or splints may aid maintenance of healthy gait and posture through limb support and alignment. Ankle-foot orthoses (AFOs) are useful to maintain optimal musculoskeletal integrity of the lower leg. AFOs are useful as client's dorsiflexion becomes weaker and the resultant foot-drop and/or ankle instability is contributing to trips, falls and abnormal gait. AFOs are most beneficial in the early stages of mobility and balance deterioration. It is recommended that MJD clients be fitted with customised AFOs (and indeed any splints or prostheses they may require) rather than "off the shelf" items, and they must be continually monitored for correct fit. As MJD progresses, patients can experience rapid weight loss and lose muscle mass, which may lead to poorly fitted orthoses. Poorly fit can cause discomfort and skin breakdowns, which themselves are painful. Further, use of orthoses by MJD patients who live in humid or hot climates must be monitored, as the climate may result in additional sweating, discomfort and skin breakdowns.

Massage, pressure, heat and acupuncture

Massage is a frequently used remedy for pain and muscle stiffness and spasms. However, clinical evidence of a beneficial effect of massage on severe pain is lacking.

Applying heat, such as use of heat packs and hot water bottles, is a common home remedy for painful ailments, particularly musculoskeletal pain. It must be noted that great care must be taken when applying heat to a patient, particularly those that may have difficulty communicating discomfort, or difficulty removing the heat themselves.

Acupuncture is a form of Chinese traditional medicine that has been used for thousands of years for the treatment of pain and other ailments. The practice of acupuncture involves inserting thin needles into specific acupuncture points (Ernst, 2006). Studies have not tested whether acupuncture is specifically beneficial for MJD patients, and whether acupuncture has any benefit for other types of pain is still an area of contention. It is hypothesised that any pain relief provided by acupuncture may be provided by a placebo effect (Ernst, 2006). It should also be noted that acupuncture needs to be performed by professionals and does have potential to produce adverse reactions. In particular, mycobacterium infections have occasionally been reported following acupuncture procedures (Xu et al., 2013).

Traditional Indigenous medicines

Traditional Indigenous medicines (also known as bush medicine) are used within many Indigenous communities to treat common illnesses and ailments. Experts in Indigenous health are starting to find that traditional Indigenous medicine holds an important place alongside western medicine because of the holistic approach that it provides and its ability to harness the spiritual factors that influence healing (Jones 2016). Aboriginal bush medicine varies between clans and regions and has involved use of a range of materials including, but not limited to, animal products, wild plants, massages and chants (Aboriginal Art online, 2000). Unfortunately little documentation or testing has been conducted on the various traditional medicines so their effectiveness or safety cannot be guaranteed. However, it is important for health care practitioners to discuss which bush medicines their patients are using to allow monitoring of these effects, as well as to respect the patient's cultural beliefs.

3.3.2 Spasticity, dystonia and muscle cramps

Physiotherapy and stretching

Physical activity, including stretching, is the most common form of non-pharmacological therapy used to treat spasticity, dystonia and cramping. Stretching exercises help maintain a good range of motion of joints, but do need to be performed at least daily. One study from 1979 found that stretching muscles three times a day could reduce cramping (Daniell, 1979). In contrast, a randomized trial containing 191 patients found no decrease in cramp frequency from stretching three times a day (Coppin et al., 2005). Passive exercise such as through the use of robot-

assisted therapy is also capable of decreasing spasticity (indicated by improved Modified Ashworth Scale scores) in patients with chronic spinal cord injury (Chang et al., 2013). Further studies to explore whether passive movement decreases severity or the frequency of episodes of spasticity in MJD patients is required.

Facilitation and passive movement

Facilitation methods, such as the Bobath approach, involves retraining muscles to enhance normal motion and decrease the amount of exaggerated reflexes (Manning, 1972). The therapy involves a therapist moving the affected limb in a repetitive manner to retrain the nervous system to allow a full range of movement and to decrease reflex responses. Ansari and Naghdi (2007) reported that unilateral Bobath approach treatment in stroke patients results in decreased spasticity on the treated side, supported by decreased motor neuron excitability.

Surgical treatments and chemodenervation

Surgical interventions for the treatment of spasticity include lengthening or releasing of tendons and muscles, denervating specific muscles and selective dorsal rhizotomy. Selective dorsal rhizotomy involves cutting of the spinal nerve roots to prevent the sensory input that triggers muscle spasms from reaching the spinal cord. This surgical treatment is sometimes used to treat spasticity in patients with cerebral palsy and spinal cord injury (Reynolds et al., 2014). Selective dorsal rhizotomy is a non-reversible treatment and involves the usual risks relating to neurosurgery.

Rather than surgically dissecting the nerve, muscle or tendon, another approach that has been used for the treatment of spasticity is injection of a paralysing agent such as Botulinum neurotoxin (see above).

3.3.3 Tremor

Relaxation techniques

It has been found that tremor is worsened during periods of stress and decreases with relaxation (Raethjen et al., 2008). Previous studies have found that relaxation techniques, including relaxation guide imagery, relaxing music, massage and spa therapy can decrease tremor in Parkinson's disease patients (Brefel-Courbon et al., 2003; Craig et al., 2006; Schlesinger et al., 2009). Schlesinger et al. (2009) found that providing relaxation guided imagery to twenty Parkinson's disease patients decreased the tremor recorded by an accelerometer for all patients included in the trial. They found that the mean amount of tremor (movements per minute) fell from a baseline level of 270 movements per minute to 35.57 movements per minute during the Relaxation Guided Imagery session. The reduction in tremor was only short-term, with subjective improvements lasting 2-14 hours after the relaxation guided imagery session finished (Schlesinger et al., 2009). Whilst the would not provide long-lasting benefit for patients, these relaxation techniques could be harnessed to reduce tremor for

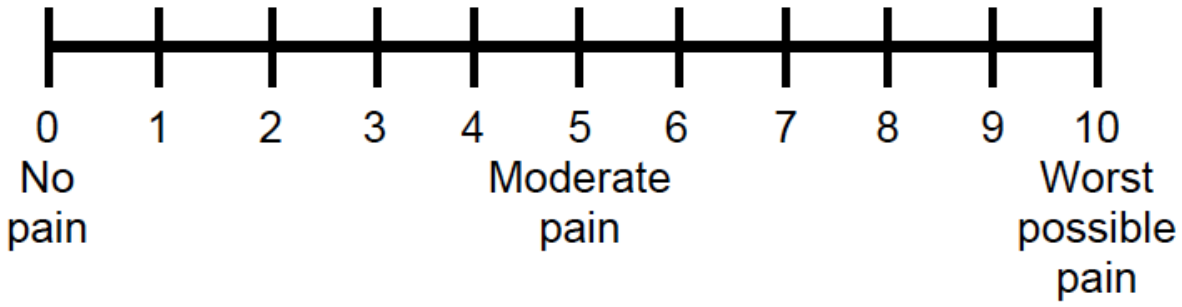
short periods to allow patients to perform fine motor tasks such as getting dressed, eating or writing.

Other therapies

In 2011, O'Connor and Kini published a systemic review (survey of current literature) on the non-pharmacological and non-surgical treatment options for patients with tremor (O'Connor and Kini, 2011). They described a broad range of studies that have tested interventions such as physical therapy, limb cooling, electrical stimulation, vibration therapy and limb weights. Unfortunately few conclusions could be made but they indicated further studies in particularly vibration therapy are warranted.

Appendix A- Pain Assessment Scales

A



B

Two popular pain rating scales are the Numeric Pain Scale (A, from McCaffery 1999) and the Wong Baker Facial Expression Pain Scale (From Wong and Baker (1988)).

Appendix B- Modified Ashworth Scale for Grading Spasticity

Grade	Description
0	no increase in muscle tone
1	slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+	slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	more marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	considerable increase in muscle tone, passive movement difficult
4	affected part(s) rigid in flexion or extension

From Bohannon and Smith (1987)

Appendix C – Unified Dystonia Rating Scale

APPENDIX 3: *Unified Dystonia Rating Scale (UDRS)*

Factor/area	Criteria
Duration	
0	None
0.5	Occasional (<25% of the time); predominantly submaximal
1.0	Occasional (<25% of the time); predominantly maximal
1.5	Intermittent (25–50% of the time); predominantly submaximal
2.0	Intermittent (25–50% of the time); predominantly maximal
2.5	Frequent (50–75% of the time); predominantly submaximal
3.0	Frequent (50–75% of the time); predominantly maximal
3.5	Constant (>75% of the time); predominantly submaximal
4.0	Constant (>75% of the time); predominantly maximal
Motor severity	
Eyes and upper face	
0	None
1	Mild: increased blinking or slight forehead wrinkling (≤25% maximal intensity)
2	Moderate: eye closure without squeezing or pronounced forehead wrinkling (>25% but ≤50% maximal intensity)
3	Severe: eye closure with squeezing, able to open eyes within 10 seconds or marked forehead wrinkling (>50% but ≤75% maximal intensity)
4	Extreme: eye closure with squeezing, unable to open eyes within 10 seconds or intense forehead wrinkling (>75% maximal intensity)
Lower face	
0	None
1	Mild: grimacing of lower face with minimal distortion of mouth (≤25% maximal)
2	Moderate: grimacing of lower face with moderate distortion of mouth (>25% but ≤50% maximal)
3	Severe: marked grimacing with severe distortion of mouth (>50% but ≤75% maximal)
4	Extreme: intense grimacing with extreme distortion of mouth (>75% maximal)
Jaw and tongue	
0	None
1	Mild: jaw opening or tongue protrusion ≤25% of possible range or forced jaw clenching without bruxism
2	Moderate: jaw opening or tongue protrusion >25% but ≤50% of possible range or forced jaw clenching with mild bruxism secondary to dystonia
3	Severe: jaw opening and/or tongue protrusion >50% but ≤75% of possible range or forced jaw clenching with pronounced bruxism secondary to dystonia
4	Extreme: jaw opening or tongue protrusion >75% of possible range or forced jaw clenching with inability to open mouth
Larynx	
0	None
1	Mild: barely detectable hoarseness or choked voice or occasional voice breaks
2	Moderate: obvious hoarseness or choked voice or frequent voice breaks
3	Severe: marked hoarseness or choked voice or continuous voice breaks
4	Extreme: unable to vocalize
Neck	
0	None
1	Mild: movement of head from neutral position ≤25% of possible normal range
2	Moderate: movement of head from neutral position >25% but ≤50% of possible normal range
3	Severe: movement of head from neutral position >50% but ≤75% of possible normal range
4	Extreme: movement of head from neutral position >75% of possible normal range

Movement Disorders, Vol. 18, No. 3, 2003

APPENDIX 3: (*Continued*)

Factor/area	Criteria
Shoulder and proximal arm (right and left)	
0	None
1	Mild: movement of shoulder or upper arm ≤25% of possible normal range
2	Moderate: movement of shoulder or upper arm 25% but ≤50% of possible normal range
3	Severe: movement of shoulder or upper arm 50% but ≤75% of possible normal range
4	Extreme: movement of shoulder or upper arm 75% of possible normal range
Distal arm and hand including elbow (right and left)	
0	None
1	Mild: movement of distal arm or hand ≤25% of possible normal range
2	Moderate: movement of distal arm or hand 25% but ≤50% of possible normal range
3	Severe: movement of distal arm or hand 50% but ≤75% of possible normal range
4	Extreme: movement of distal arm or hand 75% of possible normal range
Pelvis and proximal leg (right and left)	
0	None
1	Mild: tilting of pelvis or movement of proximal leg or hip ≤25% of possible normal range
2	Moderate: tilting of pelvis or movement of proximal leg or hip 25% but ≤50% of possible normal range
3	Severe: tilting of pelvis or movement of proximal leg or hip 50% but ≤75% of possible normal range
4	Extreme: tilting of pelvis or movement of proximal leg or hip 75% of possible normal range
Distal leg and foot including knee (right and left)	
0	None
1	Mild: movements of distal leg or foot ≤25% of possible normal range
2	Moderate: movements of distal leg or foot 25% but ≤50% of possible normal range
3	Severe: movements of distal leg or foot 50% but ≤75% of possible normal range
4	Extreme: movements of distal leg or foot 75% of possible normal range
Trunk	
0	None
1	Mild: bending of trunk ≤25% of possible normal range
2	Moderate: bending of trunk 25% but ≤50% of possible normal range
3	Severe: bending of trunk >50% but ≤75% of possible normal range
4	Extreme: bending of trunk >75% of possible normal range

Appendix D – TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS©) V 3.1

Activities of Daily Living Subscale

Rate tremor's impact on activities of daily living (0 - 4 scoring).

1. Speaking

0 = Normal.
1 = Slight voice tremulousness, only when "nervous".
2 = Mild voice tremor. All words easily understood.
3 = Moderate voice tremor. Some words difficult to understand.
4 = Severe voice tremor. Most words difficult to understand.

2. Feeding with a spoon

0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with feeding with a spoon.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot feed with a spoon.

3. Drinking from a glass

0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with drinking from a glass.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

4. Hygiene

0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with hygiene.
2 = Mildly abnormal. Some difficulty but can complete task.
3 = Moderately abnormal. Unable to do most fine tasks such as putting on lipstick or shaving unless changes strategy such as using two hands or using the less affected hand.
4 = Severely abnormal. Cannot complete hygiene activities independently.

5. Dressing

0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with dressing.
2 = Mildly abnormal. Able to do everything but has difficulty due to tremor.
3 = Moderately abnormal. Unable to do most dressing unless uses strategy such as using Velcro, buttoning shirt before putting it on or avoiding shoes with laces.
4 = Severely abnormal. Cannot dress independently.

6. Pouring

0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with pouring.
2 = Mildly abnormal. Must be very careful to avoid spilling but may spill occasionally.
3 = Moderately abnormal. Must use two hands or uses other strategies to avoid spilling.
4 = Severely abnormal. Cannot pour.

7. Carrying food trays, plates or similar items

0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with carrying food trays, plates or similar items.
2 = Mildly abnormal. Must be very careful to avoid spilling items on food tray.
3 = Moderately abnormal. Uses strategies such as holding tightly against body to carry.
4 = Severely abnormal. Cannot carry food trays or similar items.

8. Using Keys

0 = Normal
1 = Slightly abnormal. Tremor is present but can insert key with one hand without difficulty.
2 = Mildly abnormal. Commonly misses target but still routinely puts key in lock with one hand.
3 = Moderately abnormal. Needs to use two hands or other strategies to put key in lock.
4 = Severely abnormal. Cannot put key in lock.

9. Writing

0 = Normal
1 = Slightly abnormal. Tremor present but does not interfere with writing.
2 = Mildly abnormal. Difficulty writing due to the tremor
3 = Moderately abnormal. Cannot write without using strategies such as holding the writing hand with the other hand, holding pen differently or using large pen.
4 = Severely abnormal. Cannot write.

10. Working. If patient is retired, ask as if they were still working. If the patient is a housewife, ask the question as it relates to housework:

0 = Normal.
1 = Slightly abnormal. Tremor is present but does not affect performance at work or at home.
2 = Mildly abnormal. Tremor interferes with work; able to do everything, but with errors.
3 = Moderately abnormal. Unable to continue working without using strategies such as changing jobs or using special equipment.
4 = Severely abnormal. Cannot perform any job or household work.

11. Overall disability with the most affected task (Name task, e.g. using computer mouse, writing, etc)

Task _____

0 = Normal.
1 = Slightly abnormal. Tremor present but does not affect task.
2 = Mildly abnormal. Tremor interferes with task but is still able to perform task.
3 = Moderately abnormal. Can do task but must use strategies.
4 = Severely abnormal. Cannot do the task.

12. Social Impact

0 = None
1 = Aware of tremor, but it does not affect lifestyle or professional life.
2 = Feels embarrassed by tremor in some social situations or professional meetings.
3 = Avoids participating in some social situations or professional meetings because of tremor.
4 = Avoids participating in most social situations or professional meetings because of tremor.

Total for ADL Subscale _____ (48 max)

Performance Subscale

Instructions

Scoring is 0 – 4. For most items, the scores are defined only by whole numbers, but 0.5 increments may be used if you believe the rating is between two whole number ratings and cannot be reconciled to a whole number. Each 0.5 increment in rating is specifically defined for the assessment of upper limb postural and kinetic tremor and the dot approximation task (items 4 and 8). All items of the examination, except standing tremor, are performed with the patient seated comfortably. For each item, score the highest amplitude seen at any point during the exam. Instruct patients not to attempt to suppress the tremor, but to let it come out. Maximum total score is 64.

1. Head tremor: The head is rotated fully left and right and then observed for 10s in mid position. Patient then is instructed to gaze fully to the left and then to the right with the head in mid position. The nose should be used as the landmark to assess and rate the largest amplitude excursions during the examination.
   0 = no tremor
   1 = slight tremor (< 0.5 cm)
   2 = mild tremor (0.5- < 2.5 cm)
   3 = moderate tremor (2.5-5 cm)
   4 = severe or disfiguring tremor (> 5 cm)

2. Face (including jaw) tremor: Smile, close eyes, open mouth, purse lips. The highest amplitude of the most involved facial anatomy is scored, regardless of whether it occurs during rest or activation. Repetitive blinking or eye fluttering should not be considered as part of facial tremor.
   0 = no tremor
   1 = slight; barely perceptible tremor
   2 = mild: noticeable tremor
   3 = moderate: obvious tremor, present in most voluntary facial contractions
   4 = severe: gross disfiguring tremor

3. Voice tremor: First ask subject to produce an extended “aaah” sound and “eee” sound for 5 seconds each. Then assess speech during normal conversation by asking patients “How do you spend your average day?”.
   0 = no tremor
   1 = slight: tremor during “aaah” and “eee” and no tremor during speech
   2 = mild: tremor in “aaah” and “eee” and minimal tremor in speech
   3 = moderate: obvious tremor in speech that is fully intelligible
   4 = severe: some words difficult to understand

4. Upper limb tremor: Tremor is assessed during three maneuvers: forward horizontal reach posture, lateral "wing beating" posture and finger-nose-finger testing. Each upper limb is assessed and scored individually. The forward horizontal reach posture is held for 5 seconds. The lateral wing beating posture is held for 20 seconds. The finger-nose-finger movement is executed three times. Amplitude assessment should be estimated using the maximally displaced point of the hand at the point of greatest displacement along any single plane. For example, the amplitude of a pure supination-pronation tremor, pivoting around the wrist would be assessed at either the thumb or fifth digit.

Right	Left	Task
		Forward outstretched postural tremor: Subjects should bring their arms forward, slightly lateral to midline and parallel to the ground for 5 seconds. The wrist should also be straight and the fingers abducted so that they do not touch each other.
		Lateral "wing beating" postural tremor: Subjects will abduct their arms parallel to the ground and flex the elbows so that the two hands do not quite touch each other and are at the level of the nose. The fingers are abducted so that they do not touch each other. The posture should be held for 20 seconds.
		Kinetic tremor: Subjects extend only their index finger. They then touch a set object or the examiners finger located to the full extent of their reach, which is located at the same height (parallel to the ground) and slightly lateral to the midline. Subjects then touch their own nose (or chin if the tremor is severe) and repeat this back and forth three times. Only the position along the trajectory of greatest tremor amplitude is assessed. This will typically be either at the nose or at the point of full limb extension.

For all three hand tremor ratings

0 = no tremor
1 = tremor is barely visible
1.5 = tremor is visible, but less than 1 cm
2 = tremor is 1- < 3 cm amplitude
2.5 = tremor is 3- < 5 cm amplitude
3 = tremor is 5- < 10 cm amplitude
3.5 = tremor is 10- < 20 cm amplitude
4 = tremor is $\geq$ 20 cm amplitude

5. Lower limb tremor: Raise each lower limb horizontally parallel to the ground for 5 seconds. Then perform a standard heel to shin maneuver with each leg, three times. The maximum tremor in either maneuver is scored, and only the limb with the largest tremor is scored. Tremor may exist in any part of the limb, including foot.

Greatest lower limb score	
	0 = no tremor 1 = slight: barely perceptible 2 = mild, less than 1 cm at any point 3 = moderate tremor, less than 5 cm at any point 4 = severe tremor, greater than 5 cm

6. Archimedes spirals: Demonstrate how to draw Archimedes spiral that approximately fills ¼ of an unlined page of standard (letter) paper. The lines of the spiral should be approximately 1.3 cm (0.5 inch) apart. Then ask the subject to copy the spiral. Test and score each hand separately. Use a ballpoint pen. The pen should be held such that no part of the limb touches the table. Secure the paper on the table in a location that is suitable for the patient's style of drawing. Score the tremor in the spiral, not the movement of the limb.

Right	**Left**	
		0 = normal 1 = slight: tremor barely visible. 2 = mild: obvious tremor 3 = moderate: portions of figure not recognizable. 4 = severe: figure not recognizable

7. Handwriting: Have patient write the standard sentence "This is a sample of my best handwriting" using the dominant hand only. Patients must write cursively (i.e., no printing). They cannot hold or stabilize their hand with the other hand. Use a ballpoint pen. Secure the paper on the table in a location that is suitable for the patient's style of writing. Score the tremor in the writing, not the movement of the limb.
   0 = normal
   1 = slight: untidy due to tremor that is barely visible.
   2 = mild: legible, but with considerable tremor.
   3 = moderate: some words illegible.
   4 = severe: completely illegible

8. Dot approximation task: The examiner makes a dot or X and instructs the subject to hold the tip of the pen "as close as possible to the dot (or center of an X) without touching it, (ideally approximately 1 mm) for 10 seconds ". Each hand is scored separately.

Right	Left	
		0 = no tremor 1 = tremor is barely visible 1.5 = tremor is visible, but less than 1 cm 2 = tremor is 1- < 3 cm amplitude 2.5 = tremor is 3- < 5 cm amplitude 3 = tremor is 5- < 10 cm amplitude 3.5 = tremor is 10- < 20 cm amplitude 4 = tremor is > 20 cm amplitude

9. Standing tremor: Subjects are standing, unaided if possible. The knees are 10-20 cm apart and are flexed 10-20°. The arms are down at the subject's side. Tremor is assessed at any point on the legs or trunk
    0 = no tremor
    1 = barely perceptible tremor
    2 = obvious but mild tremor, does not cause instability
    3 = moderate tremor, impairs stability of stance
    4 = severe tremor, unable to stand without assistance

Total for Performance Subscale _____ (64 max)

Appendix E – A stepwise plan to the pharmacological management of neuropathic pain

Table 1
Stepwise pharmacologic management of neuropathic pain (NP)

Step 1
Assess pain and establish the diagnosis of NP [25,20]; if uncertain about the diagnosis, refer to a pain specialist or neurologist
Establish and treat the cause of NP; if uncertain about availability of treatments addressing NP etiology, refer to appropriate specialist
Identify relevant comorbidities (e.g., cardiac, renal, or hepatic disease, depression, gait instability) that might be relieved or exacerbated by NP treatment, or that might require dosage adjustment or additional monitoring of therapy
Explain the diagnosis and treatment plan to the patient, and establish realistic expectations

Step 2
Initiate therapy of the disease causing NP, if applicable
Initiate symptom treatment with one or more of the following:
- A secondary amine TCA (nortriptyline, desipramine) or an SSNRI (duloxetine, venlafaxine)
- A calcium channel α2-δ ligand, either gabapentin or pregabalin
- For patients with localized peripheral NP: topical lidocaine used alone or in combination with one of the other first-line therapies
- For patients with acute neuropathic pain, neuropathic cancer pain, or episodic exacerbations of severe pain, and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with one of the first-line therapies

Evaluate patient for non-pharmacologic treatments, and initiate if appropriate

Step 3
Reassess pain and health-related quality of life frequently
If substantial pain relief (e.g., average pain reduced to ⩽3/10) and tolerable side effects, continue treatment
If partial pain relief (e.g., average pain remains ⩾4/10) after an adequate trial (see Table 3), add one of the other first-line medications
If no or inadequate pain relief (e.g., < 30% reduction) at target dosage after an adequate trial (see Table 3), switch to an alternative first-line medication

Step 4
If trials of first-line medications alone and in combination fail, consider second- and third-line medications or referral to a pain specialist or multidisciplinary pain center

TCA, tricyclic antidepressant; SSNRI, selective serotonin and norepinephrine reuptake inhibitor.

R.H. Dworkin et al. / Pain 132 (2007) 237–251

From Dworkin et al. (2007)

Appendix F – Recommended dosages of medications for the treatment of general neuropathic pain

Prescribing recommendations for first-line medications and for opioid agonists

Medication class	Starting dosage	Titration	Maximum dosage	Duration of adequate trial
Secondary amine TCAs				
Nortriptyline, desipramine[a] (use a tertiary amine TCA only if a secondary amine TCA is not available)	25 mg at bedtime	Increase by 25 mg daily every 3–7 days as tolerated	150 mg daily; if blood level of active medication and its metabolite is below 100 ng/ml (mg/ml), continue titration with caution	6–8 weeks with at least 2 weeks at maximum tolerated dosage
SSNRIs				
Duloxetine	30 mg once daily	Increase to 60 mg once daily after one week	60 mg twice daily	4 weeks
Venlafaxine	37.5 mg once or twice daily	Increase by 75 mg each week	225 mg daily	4–6 weeks
Calcium channel α2-δ ligands				
Gabapentin[a]	100–300 mg at bedtime or 100–300 mg three times daily	Increase by 100–300 mg three times daily every 1–7 days as tolerated	3600 mg daily (1200 mg three times daily); reduce if impaired renal function	3–8 weeks for titration plus 2 weeks at maximum dosage
Pregabalin[a]	50 mg tid or 75 mg bid	Increase to 300 mg daily after 3–7 days, then by 150 mg/d every 3–7 days as tolerated	600 mg daily (200 mg three times or 300 mg twice daily); reduce if impaired renal function	4 weeks
Topical lidocaine				
5% lidocaine patch	Maximum of 3 patches daily for a maximum of 12 h	None needed	Maximum of 3 patches daily for a maximum of 12–18 h	3 weeks
Opioid agonists[b]				
Morphine, oxycodone, methadone, levorphanol[a]	10–15 mg morphine every 4 h or as needed (equianalgesic dosages should be used for other opioid analgesics)	After 1–2 weeks, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed	No maximum dosage with careful titration; consider evaluation by pain specialist at relatively high dosages (e.g., 120–180 mg morphine daily; equianalgesic dosages should be used for other opioid analgesics)	4–6 weeks
Tramadol[c]	50 mg once or twice daily	Increase by 50–100 mg daily in divided doses every 3–7 days as tolerated	400 mg daily (100 mg four times daily); in patients older than 75, 300 mg daily	4 weeks

TCA, tricyclic antidepressants; SSNRI, selective serotonin and norepinephrine reuptake inhibitor.
[a] Consider lower starting dosages and slower titration in geriatric patients.
[b] First-line only in certain circumstances; see text.
[c] Consider lower starting dosages and slower titration in geriatric patients; dosages given are for short-acting formulation.

From Dworkin et al. (2007)

Appendix G – Contributors and Reviewers

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Appendix H – Definitions

Anticholinergics	drugs that block the action of acetylcholine (ACH). ACH transmits messages in the nervous system. In the brain, ACH is involved in learning and memory. In the rest of the body, it stimulates muscle contractions. Anticholinergic drugs include some antihistamines, tricyclic antidepressants, medications to control overactive bladder, and drugs to relieve the symptoms of Parkinson's disease
Antiepileptics	also known as anticonvulsants; a class of drugs to prevent or reduce the frequency of seizures
CAG repeat	expansion of the trinucleotide CAG in a coding region of DNA that can lead to neurodegenerative disease if repeated greater than a normal range
Calcium Channel Blocker	any of a class of drugs that prevent or slow the influx of calcium ions into smooth muscle cells especially of the heart and that are used especially to treat some forms of angina pectoris and some cardiac arrhythmias—called also calcium blocker
Chemodenervation	A technique in which a pharmacologic compound (e.g. atropine, botulinum toxin) is used to paralyse a muscle or group of muscles
Dystonia	neurological movement disorder that causes muscles in the body to contract or spasm involuntarily. The involuntary muscle contractions cause twisting, repetitive and patterned movements as well as abnormal postures
Electromyography (EMG)	a diagnostic procedure to assess the health of muscles and the nerve cells that control them (motor neurons). Motor neurons transmit electrical signals that cause muscles to contract. An EMG translates these signals into graphs, sounds or numerical values that a specialist interprets.
Focal dystonia	dystonia isolated to a muscle or group of muscles in a specific part of the body; e.g. focal hand dystonia
Nociceptive pain	pain caused when nerve endings—called nociceptors—are irritated by an injury such as a cut, burn, etc.
Neuropathic pain	pain initiated or caused by injury to neural tissue in the central nervous system (CNS) or peripheral nervous system (PNS)
Opioid analgesia	also known as narcotic analgesics, are pain relievers that act on the central nervous system; they can cause side effects and lead to dependency/addiction
Spasticity	increased, involuntary, velocity-dependent muscle tone that causes resistance to movement

Appendix I – References

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The recommendations set out in this protocol are a guide only and may not be appropriate for use in all situations or with all patients. The decision whether to adopt or not adopt any of the recommendations set out in this protocol must be made by each healthcare provider on a case-by-case basis.

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