



Managing Pain and Multiple Sclerosis

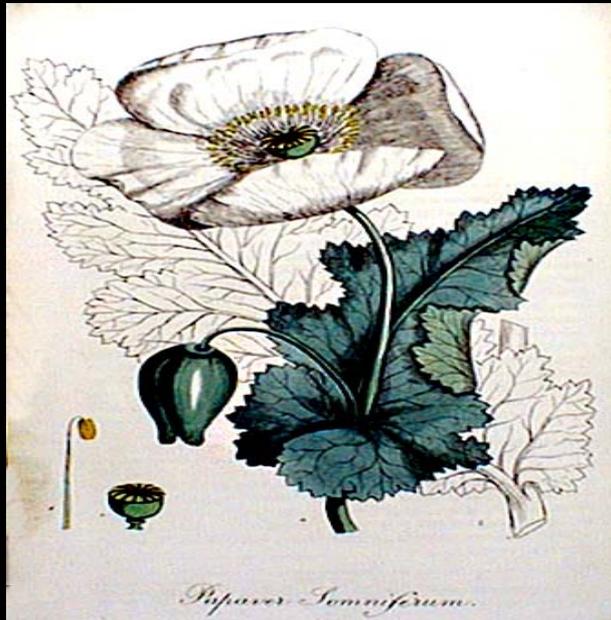
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Objectives

- Understand the nature of pain
- Describe pain in multiple sclerosis
- Discuss pharmacologic and nonpharmacologic pain management strategies
- Recognize alternative modalities used to manage MS pain



Pain is an individualistic, physiologic, learned and social response to a noxious stimuli

(Merskey, H., & Bogduk, N. (1994). International Association for the Study of Pain. *Task force on taxonomy. Classification of chronic pain (2nd ed)*. Seattle, WA: IASP Press.

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Pain is more than a symptom

“Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” (Meskey & Bogduk, IASP, 1994)

This definition suggests that pain be treated as a disease and not just a symptom.

Mostly- “whatever the experiencing person says it is, existing whenever s/he says it does” McCaffery, 1984

Pain: A Biopsychosocial Experience

- Different people experience different levels of pain in response to comparable stimuli
- Heredity, energy level, coping skills, prior pain experience-variation in tolerance
- Patients with chronic pain are more sensitive to pain and other stimuli
- Pain is a sensory, motivational and cognitive experience



Biopsychosocial Model

(Osborne et al., (2007). *Pain*, 127, 52-62.)

- Psychological and environmental factors are associated with pain intensity and interference with function
 - Perceived social support
 - Pain beliefs
 - Pain coping strategies
 - Pain-related catastrophizing
- **Pain catastrophizing:** characterizations of pain as awful, horrible and unbearable.

Gracely et al., (2004). *Brain*, 127(4), 835-843.

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Pain Coping

- Thoughts influence how we do
- Cognitive restructuring: recognizing maladaptive thinking and replacing with adaptive thoughts
- Adaptive
 - Rest and relaxation
 - Exercise
 - Reinterpreting pain sensation (burn=warmth)
 - Acceptance
 - Coping self-talk
 - Building self-efficacy for coping with pain

MS Pain: What we Know

- Pain can be traced to alterations in CNS (Nurmikko, Gupta & MacIver, 2010; Oconnor et al., 2008)
- Severe and occurring in multiple sites and more than one pain syndrome (Ehde, 2006; Pollman & Feneberg, 2008)
- Most common pain syndrome: continuous burning in extremities, headache; back pain; painful tonic spasms (Solaro et al, 2004; Moulin et al, 1987; Pollmann et al, 2004)
- Associated with increased fatigue, anxiety distress, attention, concentration, memory, learning and depression (Griswold et al, 2004; Archibald et al, 1994; Kalia & O'Connor, 2005; Gracely et al., 2004)
- Insufficiently treated, insufficient evidence for current treatments (Pollmann, 2004, 2006; OConnor et al., 2008)

Pain in MS: What we Know



- First described by Charcot in 1875

- Prevalence of pain in MS: 29%-86% (Clifford & Trotter, 1984; Moulin et al, 1987; Archbald et al, 1994; Vermote et al, 1986; Rae-Grant et al, 1999; Indaco et al, 1994; Stenager et al, 1991 & 1995; Griswold et al, 2004; Svendsen et al, 2003; Ehde et al, 2003; Pollmann et al, 2004; Indaco et al, 1994; Ehde et al, 2005; OConnor et al., 2007))
- Risk factors for development of pain: older age, longer disease duration, greater disease severity, type of MS, comorbid depression or mental health impairment (Archbald et al, 1994 ; Clifford & Trotter. 1984; Ehde et al, 2003; Hadjimichael et al., 2007; Moulin, Foley, & Ebers, 1988; Solaro et al, 2004; Svendsen, et al., 2003; Ehde et al., 2006)

MS Pain

- Psychosocial factors have greater impact than other variables on prediction of pain intensity, physical and psychological function (Osborne et al., 2006; Jensen, 2010, Ehde, 2010)
- Greater pain **severity**: increased disability, female, increased age, depression, nonstable disease course, lower education level, greater duration of pain and greater health-care utilization. (Hadjimichael et al., 2007)
- Pain interferes substantially with ADL particular to ability to work, sleep, maintain relationships and enjoy life (Warnell, 1991; Archbald et al, 1994; Pittock et al., 2004 ; Hadjimichael et al., 2007); Ehde et al, 2005; Ehde et al, 2003; Beiske et al, 2004; Svendsen et al, 2003)



Barriers to Pain Assessment and Management

- **Provider barriers**

“First, do no harm”; lack of knowledge; lack of time; fears of addiction; poor assessment; SE management and tolerance; doubt self-report; regulatory scrutiny

- **Health care system barriers**

Low priority; little reimbursement; regulatory concerns; fragmented care; lack of accountability

- **Patient barriers**

Reluctance to report; low expectations for relief; unwillingness to take meds; unwilling to accept SE; insignificant r/t other problems; negative social connotations (“good patient” syndrome); cognitive ability; poor communication; stoicism

Decade of Pain Control and Research: Assessment

- Pain is the fifth vital sign; a patient right
- **Self-report of pain is single most reliable indicator of pain**
- Include family members
- VAS and pain rating scales
- Cognitive impairment limits use of pain intensity rating scale



Brief Pain Inventory

Brief Pain Inventory

Name _____

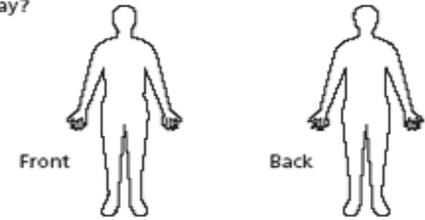
Date _____

Time _____

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, toothaches). Have you had pain other than these everyday types of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
 No pain Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
 No pain Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on average.

0 1 2 3 4 5 6 7 8 9 10
 No pain Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
 No pain Pain as bad as you can imagine

7. What treatment or medication are you receiving for the pain?

8. In the past 24 hours, how much relief have pain treatments or medication provided? Please circle the one percentage that most shows how much relief you have received.

0% 10 20 30 40 50 60 70 80 90 100%
 No relief Complete relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with you:

A. General activity

0 1 2 3 4 5 6 7 8 9 10
 Does not interfere Completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
 Does not interfere Completely interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10
 Does not interfere Completely interferes

D. Normal work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
 Does not interfere Completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10
 Does not interfere Completely interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
 Does not interfere Completely interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
 Does not interfere Completely interferes

H. Ability to concentrate

0 1 2 3 4 5 6 7 8 9 10
 Does not interfere Completely interferes

I. Appetite

0 1 2 3 4 5 6 7 8 9 10
 Does not interfere Completely interferes



MSQLI

MOS Pain Effects Scale (PES)

In the past 4 weeks, how much did these symptoms interfere with your...

	<i>Not at all</i>	<i>A little</i>	<i>Moderately</i>	<i>Quite a bit</i>	<i>To an extreme</i>
<i>1. Mood</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>2. Ability to walk or move around</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>3. Sleep</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>4. Normal work</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>5. Recreational activities</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
<i>6. Enjoyment of life</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>



Pain Journal

OLD CART

- **ONSET:** When did your pain begin?
- **LOCATION:** Where is your pain?
- **DURATION:** How long does your pain last?
- **CHARACTERISTICS:** Describe your pain
- **AGGRAVATORS:** What makes it worse?
- **RELIEVERS:** What relieves your pain?
- **TREATMENT:** What medicine do you take?

Experience of Pain

Individuals experience different levels of pain in response to comparable stimuli

- **Perceptual dominance:** the brain is capable of processing only so much information at a time
- **Pain Threshold:** the point where a stimulus is perceived as pain



Pain, a Sensory, Motivational and Cognitive Experience

- **Pain Tolerance:** duration of time or intensity of pain that is endured before initiating a response. Influenced by cultural experiences, expectations, role behaviors, and general physical and mental health. Decreased by exposure, fatigue, anger, boredom, sleep deprivation. Increased by alcohol, medication, hypnosis, warmth, distraction, strong beliefs (faith)



Pain Experience

Sensory/Discriminative

- information of strength, intensity, temporal and spatial aspects
- mediated through afferent nerve fibers, the spinal cord, the brain stem and higher brain centers
- results in prompt withdrawal from painful stimuli



Pain Experience

Motivational/Affective

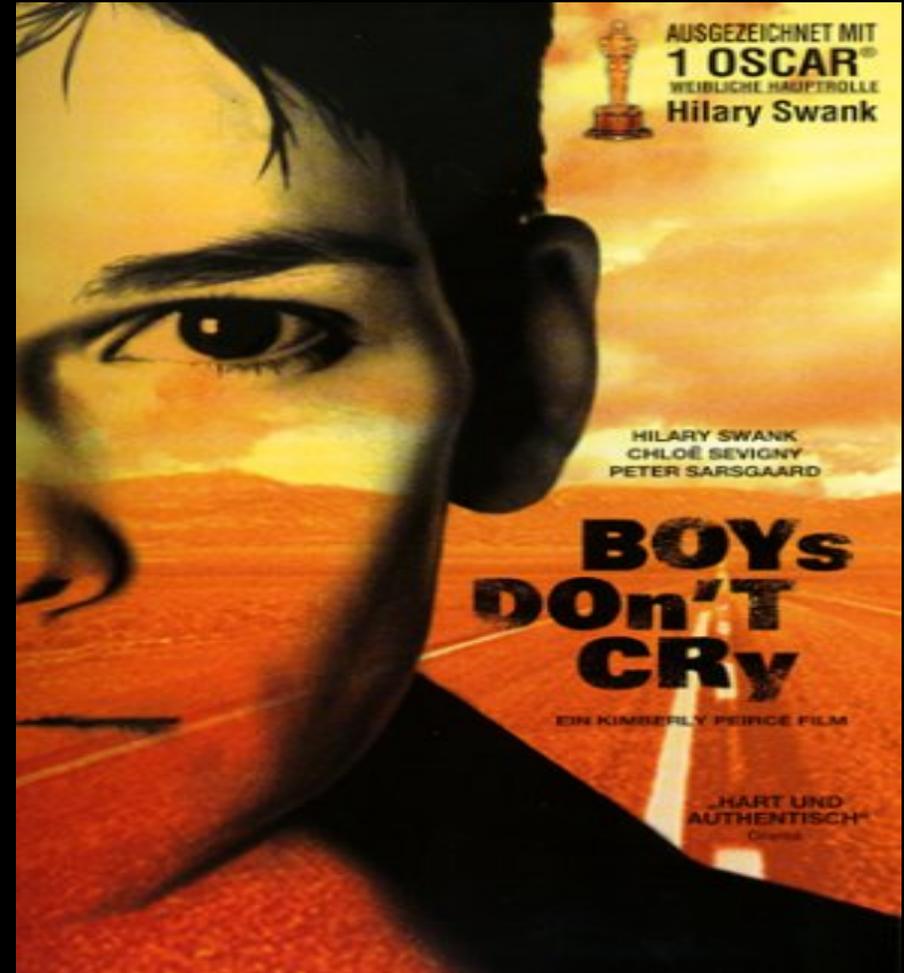
- Conditioned or learned approach/avoidance behaviors
- Mediated through interaction of the reticular formation, limbic system, and brain stem
- Life preserving behavior, “escape”, affective impulse (mood)



Pain Experience

Cognitive/Evaluative

- Over-rides learned behavior to block, modulate or enhance the pain experience
- Interpretation of appropriate behavior r/t culture, gender, and experience, role



Goals of Pain Management

- Mood
- Sleep
- Function
- Quality of life





Categories of Pain

- **Nociceptive:** Unpleasant stimuli-short acting, can be felt in one area, goes away when stimuli is removed.
- **Neuropathic/ Neurogenic:** Initiated or caused by a primary lesion in the nervous system (Merskey & Bogduk, 1994)

MS Pain is Mixed

- **Nociceptive:** disability of living with MS. Caused by any mechanism that stimulates a pain response: mechanical, thermal, chemical, electrical
- **Neurogenic:** Caused by a lesion in the CNS and may be **intermittent or steady; spontaneous or evoked**

Characterizing MS Pain

Central neuropathic pain

- **Continuous, steady pain (dysesthetic)**
 - burning, tingling, aching , throbbing –unilateral or bilateral, in extremities
 - Example: dysesthetic extremity pain
- **Intermittent (paroxysmal)**
 - shooting, stabbing, electric shock-like, and searing
 - Examples: trigeminal neuralgia



Neurogenic Pain

- difficult to manage
- often unresponsive to standard analgesic therapy
- worse at night (Moulin, Foley & Ebers, 1988), exacerbated by physical activity (Osterberg, Boivie & Thuomas, 2005) and temperature change



Mechanisms of Neuropathic Pain

Pain is transmitted by excitatory process

- Demyelination results in chemical changes
 - Upregulation of sodium channels
 - Lowered activation threshold with increase in number of sodium and calcium channels
 - Excitatory transmitters interact with NMDA receptors
 - Calcium influx and reduced GABA receptors
- Central sensitization: Hyperexcitability and neuroplastic changes
 - Spontaneous and ectopic discharges and ephaptic transmission (cross-talk), causes axonal sprouting (neuromas)

Pain is modulated by inhibitory mechanisms

Intermittent (Paroxysmal) MS Pain Syndromes

- Trigeminal neuralgia
 - 20X general population
 - 11-31% are bilateral
 - Lesions intrapontine trigeminal afferents
- Glossopharyngeal neuralgia (rare)
- Episodic facial pain
- Paroxysmal limb pain
- Painful tonic spasms (11-17%)
- Headache (prevalence: 13%-34%; 54% at dx; 22% migraine) Putski et al (2009)
- Lhermitte's (9%-40%)

Recommendations for Treatment of Trigeminal Neuralgia- Classic TN

- Carbamazepine Level A recommendation
FDA approved indication
- Oxcarbazepine Level B rating
- Lamotrigine 400 mg/d Class I study, NNT 2.1
- Baclofen 30-80 mg/d Class I and II studies

Other options with lower level of evidence:

phenytoin, clonazepam, valproic acid, pregabalin,
gabapentin,
intranasal lidocaine

Attal et al. 2006¹, Sindrup and Jensen 2002² 29

Pöllmann and Feneberg 2008, Backonja 2002,

O'Connor AB et al. 2008

Treatment of Paroxysmal Pain in MS

Trigeminal Neuralgia in MS pts

Evidence based recommendations (Pöllman and Feneberg 2008)

DRUG	REC	DOSAGE PER DAY
• Carbamazepine	A	200-1600 mg First line
• Oxcarbazepine	B	600-2400 mg First line
• Gabapentin	B	300-3600 mg
• Lamotrigine	C	25-400 mg (increase very gradually)
• Misoprostol	C	3x200 ug/d
• Valproic Acid	C	900-3000 mg
• Topiramate	C	50-400 mg
• Phenytoin	U	up to 300 mg
• Baclofen	C	25-75 mg
• Clonazepam	U	1-8 mg
• Capsaicin	U	Topical
• Amitriptyline	U	25-150 mg
• Pregabalin	U	150-600 mg

Pharmacological Management of Neuropathic Pain

Topical agents

Oral agents

Membrane stabilizing:

- Antiepileptics
- Antiarrhythmic
- Corticosteroids

Dorsal horn inhibition:

- Antidepressants
- Gaba agonists-Baclofen
- Antiepileptics

NMDA antagonists:

- Ketamine
- Dextromethorphan
- Methadone

Modulating Agents

Opioids and antidepressants



Guideline for Neuropathic Pain by IASP (updated 2007)

(Excludes TN and FM)

First line agents:

- Secondary amine tricyclic antidepressants (TCA): **nortriptyline, desipramine**
- Serotonin and norepinephrine reuptake inhibitors: **duloxetine, venlafaxine**
- Calcium channel alpha 2-delta ligand: **gabapentin, pregabalin**
- For localized np pain: **topical lidocaine**
- If acute, cancer-related, or episodic exacerbation of severe pain, and when prompt pain relief is required: **opioid analgesic or tramadol**



Treatment of Continuous Neuropathic Pain in MS

Painful Extremity Dysesthesias

Evidence based recommendations (Pöllman and Feneberg 2008)

DRUG	REC	DOSAGE PER DAY
• Amitriptyline	A	25-150 mg
• Gabapentin	A	800-3600 mg
• Pregabalin	A	75-600mg
• Lamotrigine	B	slow increase, begin 25 mg, max 400 mg
• Duloxetine	B	30-60 mg
• Opioids	B	Weak opioids: Tramadol 50-400 mg Strong: Fentanyl 200-1600 ug po, Buprenorphine 0.2-0.4mg, oxycodone 10-400 mg
• Carbamazepine	B	200-1600 mg
• Topiramate	C	25-400 mg
• Cannabinoids	B	oromucosal : THC 2.7/CBD 2.5mg/spray at avg 9.6 sprays/d [range 2-25]
• IV morphine	C	

TCA's and SSNRI

- Mainstay treatment of painful neuropathies
- **Act to inhibit reuptake of serotonin and norepinephrine**
imipramine (Tofranil®), amitriptyline (Elevil®),
nortriptyline (Pamelor®) & desipramine (Norpramin®)

ADE: sedation, hypotension, seizures,
dry mouth, weight gain

- SSNRI: Better tolerated; dual uptake; multiple receptor affinities

duloxetine (Cymbalta®)

venlafaxine (Effexor®)

ADE: nausea, dizziness, sedation,
constipation, dry mouth, anorexia; **risk of
increased LFTs**

Dosing

- duloxetine (Cymbalta®): 60 mg QD or bid
 - FDA approved for neuropathic pain
 - Pain response in first week on tx.
 - Risk for elevated AST/ALT at 2mo. of tx.
- Extended-release venlafaxine (Effexor®): 37.5mg QD , increase by 37.5mg weekly to 375mgQD
- desipramine: 25mg HS, incr. by 25mg weekly to target-200mg
- amitriptyline and nortriptyline: 10mg QD HS, incr. by 10mg weekly to target- 150mg/d

Antiepileptics (AED's)

- Trousseau coined “neuralgic epilepsy” in 1853
- Phenytoin used to tx. pain in early 40's
- Carbamazepine used for TN pain in 1968
- Now, third generation antiepileptics
- **Acts to block Na⁺ or Ca⁺⁺ channels**
- **Nerve membrane stabilizing agents**
- **SE: sedation, dizziness, rash, fatigue, diplopia, liver toxicity (side effects minimized with long acting formulas)**

Antiepileptic Drugs

- carbamazepine (Tegretol®, XR)-assoc c neural tube defects **Preg Cat: D**
- phenytoin (Dilantin®)-hirsutism, gingival hyperplasia, constipation
- valproic Acid (Depakene®) **Preg Cat.: D** tremor; wt. gain
- clonazepam (Klonopin®) **Preg Cat: D** anticholinergic

Third generation antiepileptic drugs are better tolerated, have fewer drug interactions and less affect on cognitive function

- gabapentin (Neurontin®) 900 titrated to 3600mg tid **1/1000 suicide**
- tiagabine (Gabitril®) up to 56mg/d in 2-4 divided doses
- lamotrigine (Lamictal®)-rash in 10%-hypersensitivity rx/ MS tials
- topiramate (Topamax®) wt. loss; incr. fluids; affects cognition
- oxcarbazepine (Carbatrol, Trileptal®), XR) **Preg Cat: D**
- pregabalin (Lyrica®)100mg tid(2-10X more potent than neurontin) schedule V, “high” like valium- withdrawal headache and nausea
- felbamate (Felbatol®), aplastic anemia, acute hepatic failure, cardiotoxic
- levetiracetam (Keppra®) recent MS trials of pain showed an effect
- zonisamide and vigabatrin less cognitive impact, hypersensitivity

gabapentin (Neurontin®)

- Mechanism: Ca⁺⁺ channel blocker
- Small clinical trials in MS, good reduction in pain both spontaneous and evoked (Khan et al, 1998; Solaro et al, 1998; Guay et al, 1998; Houtchens et al, 1997)
- **Best for: cramping, throbbing, pins & needles**
- Poor response for dull aching pain
- Dose: average 600 to 2400, up to > than 3600mg/d
- ADE: blurred vision, fluid retention, nausea, dizziness, confusion (dose related)
- Renal excretion; no drug-drug interaction
- Decr. absorption at incr. doses

pregabalin (Lyrica®)

- Gabapentin analogue; “son of gabapentin”
- Lower doses= fewer ADE
- Renal excretion
- Excellent absorption
- Does not require titration
- Studies indicate not much benefit above 300mg/d (100mg tid)
- Additive wt gain and edema with TZDs
- Controlled schedule V
- Withdrawal headache and nausea

topiramate (Topamax®)

- Multiple mechanisms: block Na⁺ and Ca⁺⁺; blocks glutamate; potentiates GABA
- Small study in MS: 50% pain relief
- Titrate slowly
- ADE: wt. loss, psychomotor retardation; ataxia, drowsy, dizzy, memory and language problems
- Avoid use with acetazolamide (black box)
- May decrease effectiveness of OCs

levetiracetam (Keppra®)

- MS trials for spasticity (effect in phasic spasticity not tonic)
- Mechanism: Ca⁺⁺ channel blocker
- ADE: edema, ataxia, agitation, depression, anxiety
- Avoid abrupt cessation

tiagabine (Gabatril®)

- Mechanism: GABA reuptake inhibitor
- MS trials show effect on neuropathic pain
- Titrate slowly, take with food, avoid abrupt cessation; do not use concomitant with carbamazepine
- ADE: serious rash; confusion; concentration difficulties, nervousness, tremor

lamotrigine (Lamictal®)

- Trials in MS with effect on burning paresthesias (McCleane et al, 1998)
- Mechanism: membrane stabilizing, Na⁺ channel block; agonist on GABA
- No effect on cognition or arousal
- Long slow titration by 25mg increments to effect, max dose:400mg/d
- ADE: Skin rash (life threatening), ataxia, headache, dizziness, somnolence
- Poorly tolerated

Antiarrhythmics

- mexilitine (Mexitil®) Study in MS pain: 300mg-400mg QD
sodium channel modulator

SE: palpitations, chest pain, tremor, GI, dizziness double vision, nervousness

- Lidocaine crosses BBB easily; study in paroxysmal itch and tonic seizures
- Alpha 2 adrenergic agonists
 - Clonidine
 - Tizanidine (LFTs baseline, 1-3-6 months)

Topical Agents

- capsaicin (Zostrix®): 0.025%, 0.075% 4X/d
SE: burning, sneezing, coughing

Transdermals:

- fentanyl (Duragesic®), buprenorphine
- lidocaine/prilocaine (EMLA®)
- lidocaine patch 5% (Lidoderm®) max 3 patches/d, 12h
- Diclofenac
- methylsalicylate
- aspirin Cream
- clonidine Gel (0.05% qid)
- application of heat and cold
- pressure

Evidence for Cannabis in MS

- **Delta(9)-Tetrahydrocannabinol (THC):**
(dronabinol®), (Marinol®) PO 10mg;

Delta(9)-THC & cannabidiol:

Sativex® (mouth spray)

- SE(mild): dry mouth, dizziness, somnolence, nausea, intoxication
- . Evidence links cannabis with depression, panic attacks and psychosis---the therapeutic benefit may be small compared to ADE



FDA RULES ON MEDICAL MARIJUANA April 20, 2006

“ There **is** sound evidence to support that smoked marijuana is harmful”

- Marijuana is Schedule I of Controlled Substance Act

(meets 3 criteria)

- High abuse potential
- No currently accepted medical use
- Lack of safety

Cannabis/Cannabinoids in MS

- US: 14 states have passed laws eliminating criminal penalties for using marijuana (MJ) for medical purposes
- **Federal Controlled Substances Act (CSA)** classifies MJ as **Schedule I** – high potential for abuse, no currently accepted medical use
 - Criminalizes prescribing, dispensing and possession of MJ for any purpose
- Oct. 2009: Dept of Justice issued *memorandum that federal resources should not be used to prosecute persons whose action comply with states' law permitting medical use of MJ*



Cannabis RCT in Multiple Sclerosis

- Effect on : MS pain, spasticity, tremor; bladder
- Twenty-five short term trials of oral, oro-mucosal delivery of Delta-9-tetrahydrocannabinol in combination with Cannabidiol (Consroe, 1997; Smith et al 2002, 2004, 2005; Croxford et al, 2003; Pertwee et al, 2002; Wade et al, 2004; Baker, 2000; Killestein et al, 2002, 2004; Young & Rog, 2003; Fox et al, 2004; Zajicek CAMS study, 2005; Barnes, 2005; Freeman et al 2006; Ben Amir et al 2006; Perras, 2005; Rog, 2005; Robson, 2005; Svendsen et al, 2004; Barclay, 2004; Voth & Schwartz, 1997; Clark et al 2004; Vaney et al, 2004; Brady et al, 2004)
- ADE: dry mouth, dizzy, nausea, intoxication, somnolence
- **Conclude: modest treatment effects; good add on drug; mild ADE; well tolerated; no support for long term use**
- Comparison with codeine similar effect but TCH > psychotropic ADE (Kinzbrunner et al, 2002).
- Research of effect on immune system (Killestein et al, 2003, Baker et al, 2003; Malfitano et al, 2005; Katona et al, 2005; Pryce, 2005;

Cannabinoids in Multiple Sclerosis

- Multiple trials incl. RCTs of oral agents and oro-mucosal delivery, incl. THC, CBD, and combinations THC/CBD
(Consroe, 1997; Smith et al 2002, 2004, 2005; Croxford et al, 2003; Pertwee et al, 2002; Wade et al, 2004; Baker, 2000; Killestein et al, 2002, 2004; Young & Rog, 2003; Fox et al, 2004; Zajicek CAMS study, 2005; Barnes, 2005; Freeman et al 2006; Ben Amir et al 2006; Perras, 2005; Rog, 2005; Robson, 2005; Svendsen et al, 2004; Barclay, 2004; Voth & Schwartz, 1997; Clark et al 2004; Vaney et al, 2004; Brady et al, 2004)
- Effect on : **MS pain, spasticity, tremor; bladder control**
- ADE: dry mouth, dizzy, nausea, intoxication, somnolence
- Comparison with codeine similar effect but THC > psychotropic ADE (Kinzbrunner et al, 2002).
- **Conclude: modest treatment effects; consider as add on drug; mild ADE; well tolerated; uncertain for long term use**
- IASP (2007): level A evidence, but second line:
 - lack of long-term f/u data
 - Limited availability
 - Concern for precipitating psychosis/schizophrenia



When Are Opioids Indicated?

- Pain is moderate to severe
- Pain has significant impact on function
- Pain has significant impact on quality of life
- Non-opioid pharmacotherapy has been tried and failed
- Patient agreeable to have opioid use closely monitored (e.g. pill counts, urine screens)
- Patient has acceptable risk profile



Opioids

- Most potent and effective analgesia
- Mu agonist isolated from opium 100 yrs ago
- Reduce Ca⁺⁺ influx
- Hallmark of use: individualize tx.
- Care in patient selection; written agreement
- Long acting agents best
 - morphine
 - oxycodone
 - fentanyl
 - methadone

Opioids: Methadone

- Mechanisms of action: **Mu receptor agonist; NMDA antagonist**; inhibits reuptake of 5HT, NE
- Suppresses opioid withdrawal symptoms > 24 hours
- **For analgesia: “Short-acting”**
 - Onset 30 - 60 mins, peak 1-2 hours, duration 4-6 hrs+
 - Needs to be given TID to QID
- Long half-life: accumulation over 1 wk; not for “prn” use
- Difficult to titrate, go slow
- Starting dose: 2.5 to 5 mg bid
- Equianalgesic dosage – unreliable
 - Roughly about 20% of morphine dose
 - Not linear: low dose 1:4, higher dose (>300 mg morphine equiv) 1:12+
 - Acute: methadone 20 mg = morphine 30 mg
 - Chronic: methadone 2-4 mg = morphine 30 mg
- Inexpensive (5mg tid= \$8.00/month)
- ADE: pruritis, sweating, flushing; sleep apnea (?), cardiac toxicity (QTc prolongation, arrhythmia, torsades⁵³)

Opioids: Fentanyl Patches

Fentanyl TD = *Duragesic*®

- Patches of 12, 25 $\mu\text{g/hr}$ to 100 $\mu\text{g/hr}$ applied topically
- Fentanyl 25 $\mu\text{g/hr}$ equals about 50-60 mg morphine/day
- Use official conversion ratios to begin fentanyl patch
- Patient has to be on minimum of 60 mg morphine equivalent per day to begin fentanyl
- Patch cannot be cut, but folded to decrease dosage
- Onset after 12 - 16 hrs
- Change Q72 h, effectiveness may drop off on the 3rd day
- Heat increases absorption and drug effect
- Steroid topical agent (inhaler) may prevent skin irritation
- NOT detected on routine urine drug screen for opiates
- Advantages: not dependent on GI absorption, good in dysphagia patients, less constipating.

Evidence for Opioid Use in Neuropathic/Neurogenic Pain

Cochrane meta-analysis of RCT 1966-2004:

- significant efficacy of opioids over placebo for neuropathic pain
- Primary outcome- VAS (30%-50% decr. pain intensity or 2 points on VAS)
- ADE are common: nausea, constipation, drowsiness, vomiting, dizziness
- Further RCT needed to establish long-term efficacy, safety, addiction/abuse potential, and effects on QOL

Eisenberg, E., McNicol, E., & Carr, D. (2005) JAMA, 293 (24), 3043.

Opioid Use in MS Neurogenic Pain

- Kalman et al, 2002: poor response (28%) at high dose only; does not support routine use in MS
- Rowbotham et al, 2003 NEJM, 348 (13), 1223: less responsive than peripheral pain
8 MS had 36% reduction in pain at high dose levorphanol
- Attal et al, 2002. Neurology, 58, 554: ineffective in spontaneous, ongoing pain, significant decrease in evoked pain

Opioid Analgesics: Side effects

- Most serious: respiratory depression
- Most common: constipation, sedation/mental clouding,
- Less common: nausea, pruritus, dry mouth, sweating, urinary retention
- Most side effects diminish over time. Exception: constipation
- Bowel regimen in all pts with chronic opioids
 - **Senokot ® (senna + colace) 2 tabs BID. Increase to 3-4 TID; Alternative: Lactulose**
 - **Dulcolax (Bisacodyl) prn, Polyethylenglykol (Miralax) prn**
- Longer term use: amenorrhea, sexual dysfunction, decreased testosterone level, osteoporosis, immune suppression, sleep apnea
- opioid induced hyperalgesia

Opioids: Tramadol and Tapentadol

- **Tramadol** = *Ultram*®
 - Major metabolite is weak μ -opioid agonist
 - Norepinephrine and serotonin reuptake inhibitor
- RCT in PHN, DPN, mixed neuropathies, post-amputation
- ADEs: dizziness, nausea, constipation, somnolence, orthostatic hypotension, increased risk of seizures
- Drug interaction: antidepressants, esp. SSRI, MAO-I
- Begin as 50 mg once or twice daily, max. 100 mg tid to qid, available in short and long-acting formulations
- Low risk of abuse, but not negligible, and may be rising

- **Tapentadol** = *Nucynta*®
 - Dual action: μ -opioid agonist and NE reuptake inhibition
 - FDA approval 2008 for moderate to severe acute pain⁶⁸

A Case for Polypharmacy

Na ⁺ channel modulators	Ca ⁺⁺ channel modulators	Inhibit reuptake of NE and 5HT	Gaba agonists	NMDA agonist
CBZ OXC, PHT mexilitine lodocaine lamotrigine topiramate zonisamide	gabapentin topiramate pregabalin levetiracetam ziconitide zonisamide	imiprimine desiprimine amitriptyline nortryptiline tramadol venlafaxine duloxetine	baclofen zonisamide lamotrigine vigabatrin	ketamine dextromethorphan methadone memantine

Summary of Treatment Suggestions

What do YOU want to use?

32 y/o f with MS and severe dysesthesia pain in legs that...

- ... appears depressed and c/o poor sleep? **Tricyclics (TCA)**
- ... is severely depressed and overweight? **SNRI: dulox/venlafaxine**
- ... wants "something as safe as possible"? **gabapentin/pregabalin**
- ... has medical co-morbidities, many meds? **gabapentin/pregabalin**
- ... has bipolar disorder, is hypomanic? **lamotrigine**
- ... has headache and depression? **Tricyclics (TCA)**
- ... has migraines and is overweight? **topiramate**
- ... also has trigeminal neuralgia? **carbamazepine/oxcarbazepine**
- ... also has TN and many medical issues? **gabapentin, pregabalin**
- ... has severe flare-ups lasting for days? **prn tramadol**
- ... severe flare ups and is on high dose SSRI? **prn oxycodone**

Treatment Recommendations

- Start with a low dose and gradually increase or titrate to efficacy
- If partial pain relief occurs with one drug, a combination of two or more drugs can often yield better results with fewer side effects
- In general, when pain free for 3 months on treatment, consider a slow taper.

Steady MS Pain Syndromes

- Dysesthetic extremity pain
 - Most common chronic pain syndrome
 - Persistent, burning, tingling, dull, nagging, prickling-associated with warmth
 - Worse at night and after exercise
 - Aggravated by changes in temperature
- Musculoskeletal pain
 - Back pain
- Painful tonic spasms
 - Triggered by touch, movement, hyperventilation, emotions
 - Occur several times in a day for < 2 min

Chronic Musculoskeletal Pain

Causes

- weakness
- stress on bones, joints and muscles
- immobility
- improper use of compensatory muscles
- steroid induced osteoporosis
- avascular necrosis
- disc disease-always follow up- do not assume everything is MS

Dysesthetic Extremity Pain

Treatment

- Most common chronic pain syndrome
- Persistent, burning, tingling, dull, nagging, prickling-associated with warmth
- Worse at night and after exercise
- Aggravated by changes in temperature

- Tricyclic antidepressants-drugs of choice
- Antiepileptics
- Topicals-capsaicin, clonidine
- Warm or cold compresses
- Pressure stockings
- Cooling
- Lambskin booties at night
- Bed cradle to keep sheets off

Treatments

- Medication-NSAIDS
- Position change and proper support
- Prevention
- Physical therapy is 'key'
- Stress induced analgesia
- Exercise
- Cutaneous stimulation
 - Massage
 - Vibration
 - Heat and cold
 - Therapeutic touch
 - TENS

Drugs for Nociceptive Pain

- salicylate (Aspirin®) PO 1600mg bid max
- acetaminophen (Tylenol®) PO up to 2- 4g/d (toxic at 5-8g/d)
- NSAIDs: indomethacin (Indocin®), ibuprofen (Motrin®), Nuprin, Advil®), naproxen (Aleve®, Naprosyn®), diclofenac (Voltaren®), sulindac (Clinoril®), oiroxicam (Feldene®), ketoprofen (Oruvail®), nabumetone (Relafen®) peripheral prostaglandin antagonism
- **Action:** inhibit production of prostaglandin which protect the lining of the stomach, ensure adequate renal function, maintain balance in CNS so NSAIDs can cause GI irritation and bleeding, renal insufficiency, edema, hypertension, and CNS imbalance
- **Contraindicated:** renal dz, bleeding disorders, hypersensitivity (allergy to ASA, nasal polyps, asthma)

Easier on the Stomach

- misoprostol (Cytotec®) is a synthetic prostaglandin to protect GI (SE: diarrhea) PO bid
 - diclofenac + misoprostol (Arthrotec®)
 - H2 blockers and proton pump inhibitors
 - COX 2 inhibitor selective agents: celecoxib (Celebrex®)
 - Side effects: CVD, edema, GI, incr LFT
 - Caution: CYP2C9 (fluconazole) and CYP2D6
 - **SE management:** antacids, PPI, H2 agonists
- Pregnancy Category:** B (acetaminophen, ketoprofen, naproxen, flurbiprofen, diclofenac, diflunisal; C (the rest);
D (salicylates); X misoprostol

NSAIDs Rules To Live By

- Use exactly as prescribed
- LFTs at baseline and periodically: DC if abnormal LFTs persist or worsen. ALT may be the most sensitive indicator of NSAID induced liver dysfunction
- Long term use incr. risk of heart attack and stroke and GI bleed
- Ulcer risk incr. with steroids, anticoagulants, longer use, smoking, ETOH, age and poor health

Management of Spasticity

Botox and the Usual Suspects

(baclofen, tizanidine, clonazepam, gabapentin, dantrolene, & diazepam)

Botulinum Toxin (BTX-A)

A toxic enzyme that causes local, temporary, cholinergic chemodenervation

- FDA approved for: strabismus, blepharospasm, cervical dystonia, and cosmetic, spasticity
- Non FDA uses: tremor, dystonia
- Botulinum Toxin Type A: Lyophilized powder 100 U per vial
- Side effects: pain and weakness
- Nonresponse: low dose; injection technique; storage and reconstitution; muscle involvement changed; NAB+



Nonpharmacological Treatments

- **Psychological**

- Cognitive-behavioral approaches (education, relaxation, psychotherapy, imagery, hypnosis, biofeedback; support groups; distraction; recreation; laugh therapy; meditation)

- **Physical agents**

- superficial heat and cold; physical therapy; stretching; reconditioning to improve strength, endurance, flexibility; pressure; counter-irritation; massage; exercise; attention to ergonomics; immobility; electroanalgesia; acupuncture; sound nutrition; yoga; tai chi; music

- **Surgical**

Invasive Intervention

Motor Cortex Stimulation (neuromodulatory)

Regional Nerve Blocks

- Phenol/alcohol nerve ablation-destroys the nerve, may cause neuroma
- Botulinum toxin; local anesthetics; corticosteroids

Intraspinal Therapy (intrathecal pumps)

- Epidural: spinal opioids, baclofen
- Dorsal root entry zone: neuro stimulation

Neurosurgical Procedures (spinal cord)

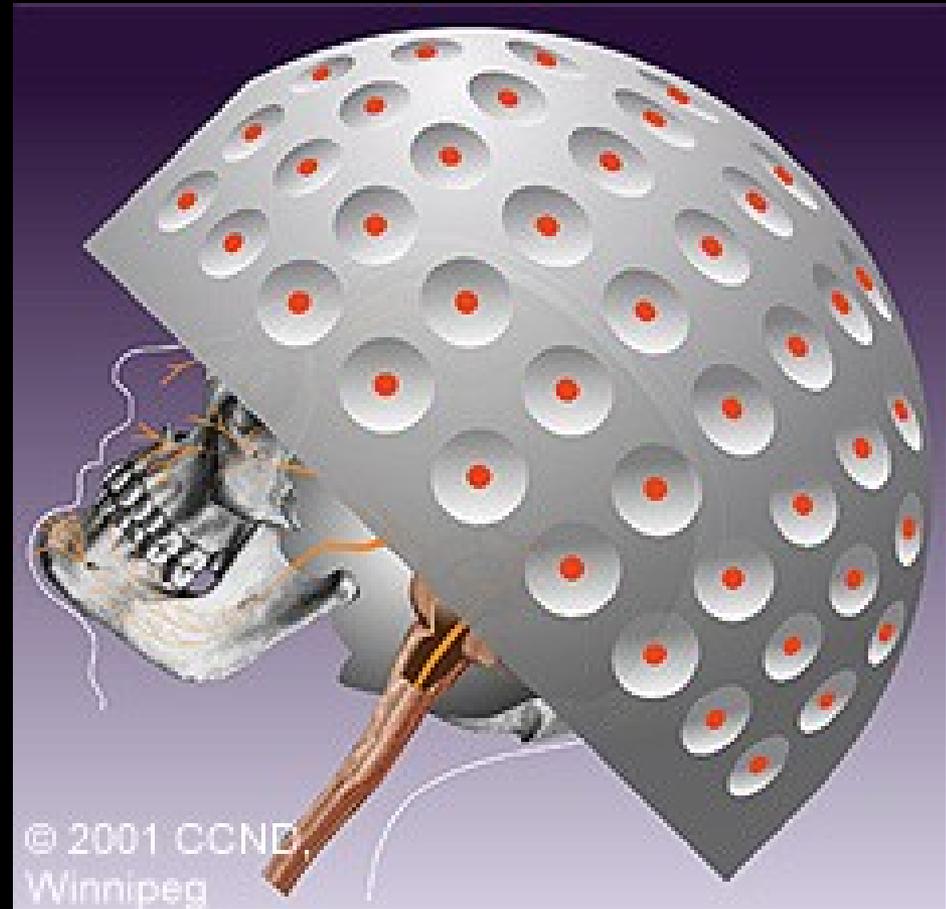
- Cordotomy (hot probe to spinal cord)
- Rhizotomy-percutaneous radiofrequency rhizotomy

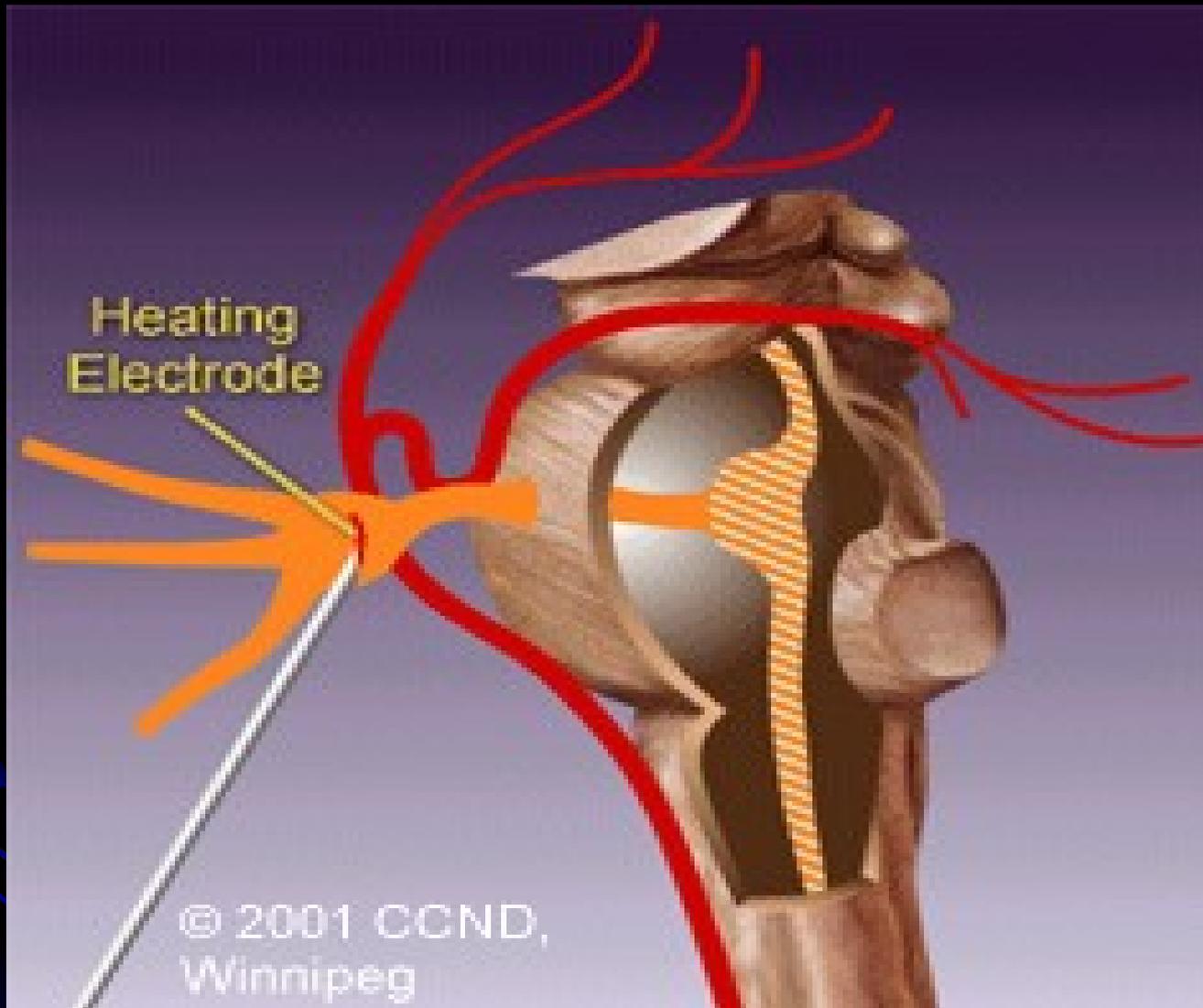
Neurosurgical procedures -brain

- Omayya reservoir: Morphine can be infused into the cerebral ventricles
- Radiosurgery-Gamma knife-Dedicated linear accelerator (LINAC)

Gamma Knife Radiosurgery

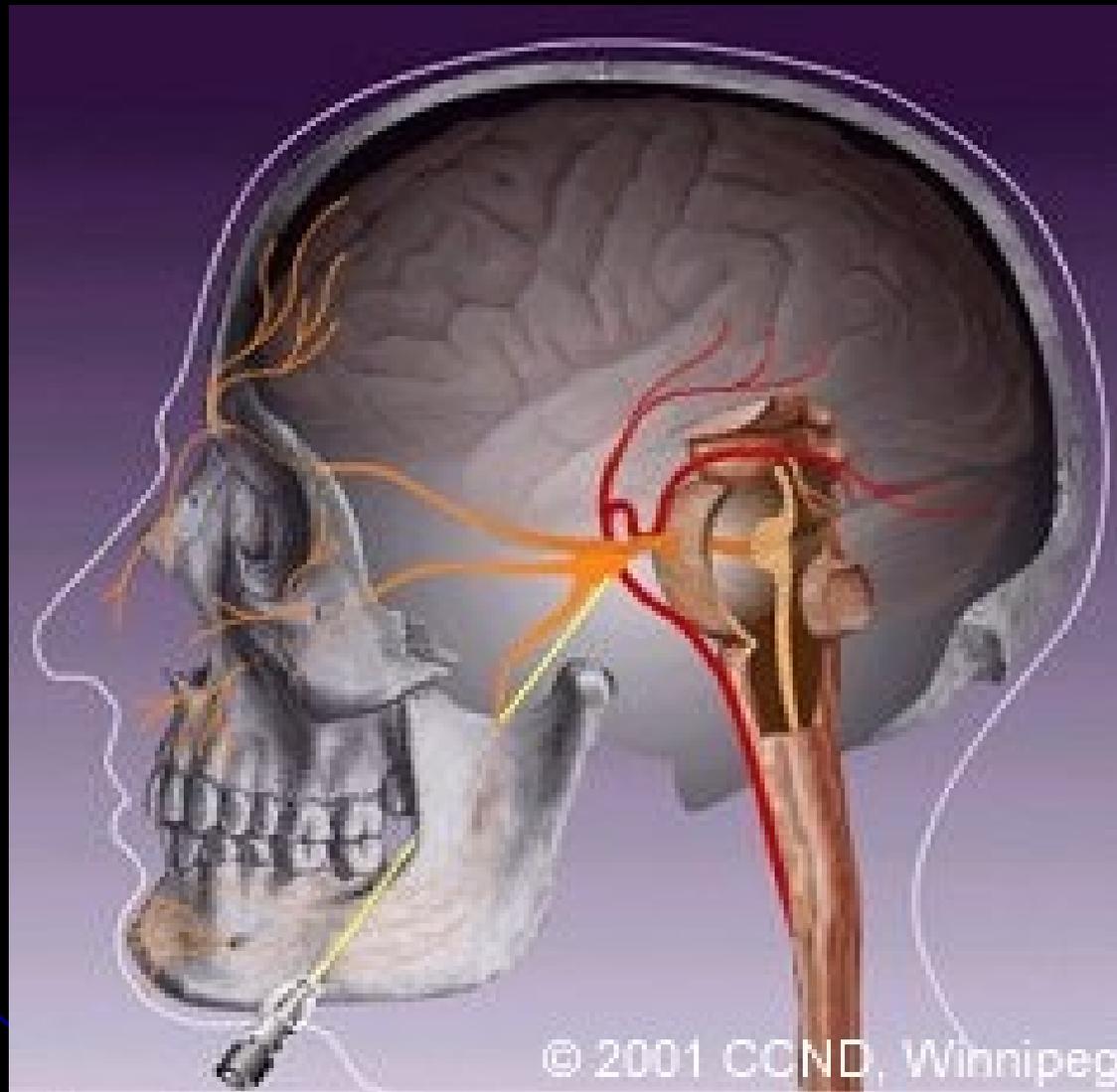
- Minimally invasive
- Relief with lag of one month
- Zorro et al., (2009). *Neurology*, 73(14), 1149-54.
 - 37 pts over 12yrs
 - 62.1% complete pain relief
 - Reasonable pain control in 97.3% and after 5 yrs in 54%
 - Nondisabling paresthesias in 5.4%
 - 14 pts underwent a second procedure





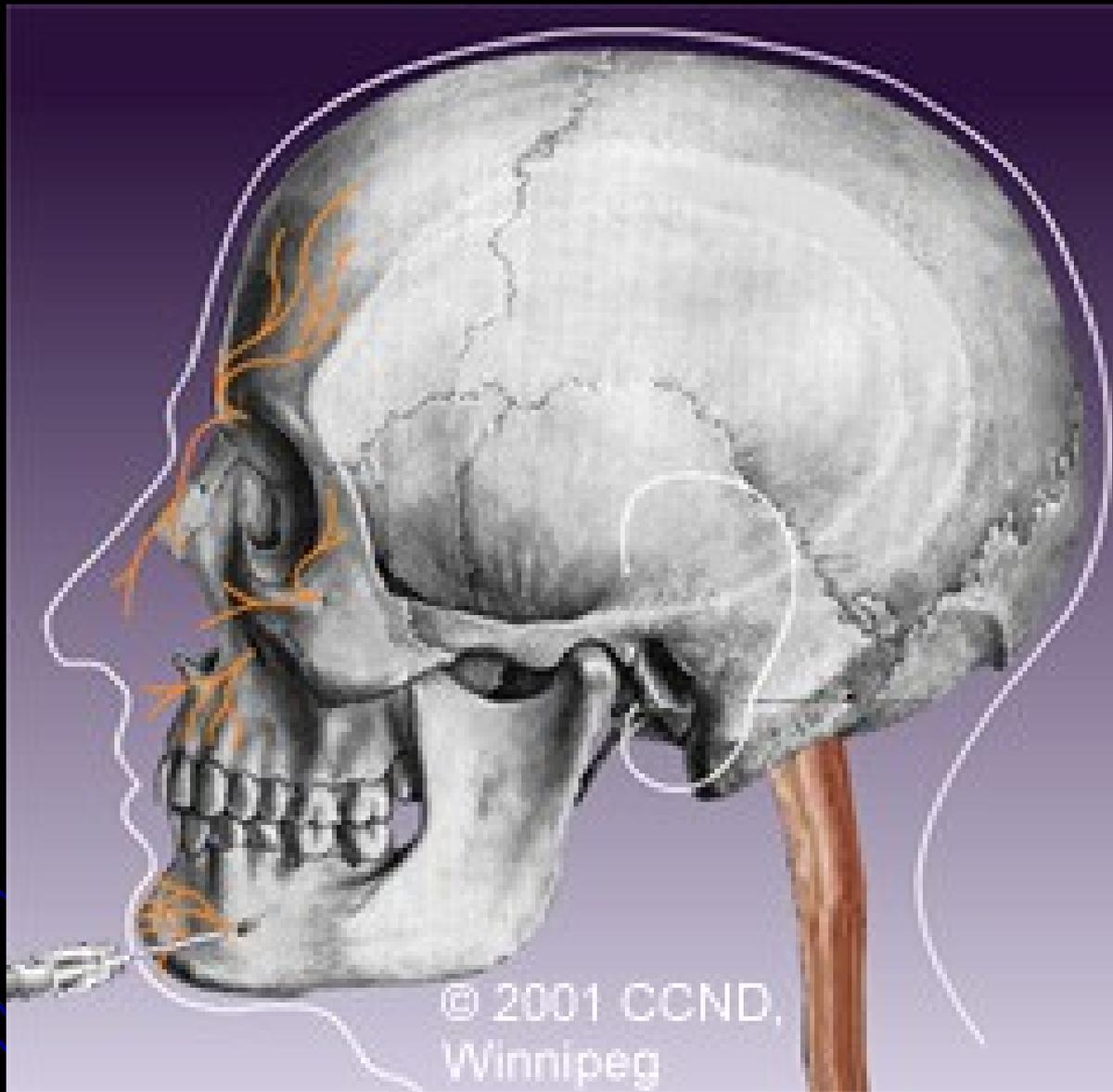
Radiofrequency Rhizotomy

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Percutaneous Rhizotomies

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Peripheral Trigeminal Nerve Blocks, Sectioning and Avulsions

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Noninvasive Mechanical Modalities

- Anodal transcranial direct current stimulation had significant reduction in VAS scores. Mori et al., (2010). *Journal of Pain*, 11(5), 436-442.
- Transcutaneous electric nerve stimulation

Alternative Therapies used by Patients for Pain Management

- CAM
 - What is the treatment?
 - What does it involve?
 - How does it work?
 - Why does it work?
 - Are there any risks?
 - What are the side effects?
 - Is it effective? (Ask for evidence or proof!)
 - How much does it cost?

CAM for Pain

- Acupuncture
 - Reflexology
 - Massage
 - Chiropractic
 - Cannabis
 - Relaxation techniques
 - Hypnosis
 - self-hypnosis training (Jensen et al., 2009)
- } Most commonly utilized



Managing Your Pain

Taking Ownership

- Keep a pain diary
- Talk about your pain at each doctor visit
 - When does it begin; Where is it located; How long does it last
 - What does it feel like; what aggravates your pain
 - What makes your pain better
 - What are you using to treat your pain- **meds, alternative treatments, over-the-counter etc**
- How does your pain affect your life: Mood, sleep, relationships, ability to work and play?
- Are you having any side effects from medications you use for pain?

Considerations when you are not getting relief

- May not be MS pain
- Drug interaction
- Psychosocial issues
- Referral to pain specialist/clinic
- Mechanical/skeletal problems
- Offer resources

www.painaid.painfoundation.org; www.ampainsoc.org;
www.mayoclinic.com; www.pain.com; www.painmed.org;
www.aapainmanage.org; www.abpm.org; www.theacpa.org

Treatment of Neuropathic Pain

General considerations

- Medication therapy should be **in the context of non-pharmacological treatment** incl. coping methods (CBT), stress reduction, sleep hygiene, PT, and interventional procedures
- Discuss **realistic expectations**, set measurable functional goals
- Individual variation in the response to medications is substantial
- Overall approach: stepwise process to identify the medications that provide the greatest relief with fewest adverse effects.
- If medication is not effective or causes intolerable side effects, d/c it
- If medication provides partial relief and is well tolerated, add on second agent with different mechanism of action.
- **“Rationale polypharmacy”**:
 - use agents with different mechanism of action
 - potential for additive analgesic benefits with less ADEs
 - combine agent with rapid benefit with one that requires weeks
 - but: consider added cost, lower compliance, drug interactions etc.

Dworkin RH, et al; Pain 2007 Dec 132 (3):237-51

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The End... Questions?

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Neuropathic Pain Algorithm

Disease specific measures

Symptom management

**use of
disease
modifying agents**

regional/local tx.

Systemic tx.

topical regional stimulation rehab ablative

drug tx

behavior tx

Capsaicin
Emla
Lidocaine
Clonidine
gel

sympathetic
nerve block
epidural/
intrathecal
blocks or pumps
selective nerve
root blocks

TENS
acupuncture
massage
spinal stim.

ROM
splinting
assistive
devices
ergonomics

phenol/
alcohol
nerve ablation
cordotomy
rhizotomy
Gamma knife

anticonvulsants
tricyclic
antidepressants
Clonazepam
Mexiletine
Corticosteroids
Opioids
Cannabis
Tramadol

biofeedback
hypnosis
distraction
relaxation
guided
imagery

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World Health Organization

W H O

- individualize the regimen
- use simple, least invasive
- medicate by the clock
- use the WHO ladder-additive tx.
 1. Mild to moderate pain: Tylenol or NSAID
 2. Persistent pain: adjuvant and/or mild opioid
 3. Moderate to severe pain: increase dose, increase potency

Definitions

- **Allodynia:** Pain arising from a stimulus that does not normally evoke pain
- **Analgesia:** Absence of pain in response to stimulation that would normally be painful
- **Dysesthesia:** An unpleasant abnormal sensation either spontaneous or evoked
- **Hyperanesthesia:** Increased sensitivity to stimulation
- **Hyperalgesia:** Increased response to a stimulus that is normally painful

- **Hyperpathia:** painful syndrome of increased reaction to a stimulus and increased threshold
- **Hypoalgesia:** diminished pain in response to normally painful stimulus
- **Neuropathic:** disturbance of function or pathologic change in a nerve (peripheral, central, autonomic)
- **Nociceptor:** A receptor sensitive to noxious stimuli
- **Pain threshold:** when a stimulus is perceived as pain
- **Pain tolerance:** duration or intensity endured before initiating treatment
- **Paresthesia:** an abnormal sensation, whether spontaneous or evolved