



# Challenges in Managing Rheumatological Disorders in the Workplace – the impact of Newer Treatments

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April 9<sup>th</sup>, 2010

# Purpose

- To inform about current approaches to treatment of inflammatory arthritides such as rheumatoid arthritis, especially in the context of occupational health
- To discuss approaches to fibromyalgia and related disorders to maximize function especially in the context of occupational health

# New Treatments and Approaches in Inflammatory Arthritis

- Rheumatoid arthritis (RA) is the most common form of inflammatory arthritis
- Prevalence rate ~ 1%, annual incidence 3/10,000 adults
- Patients with RA often absent from work, decrease routine work hours or suffer from job loss
- Many unable to work at full potential while at work, 'presenteeism'

# Associated costs

- Productivity losses account for 32% total annual cost per RA patient in Europe
- Medical costs 21%
- Drug costs 14%
- Non-medical costs 14%
- Informal care costs 19%

# Work absence can occur early

- Within first 3 years of RA, average of 82 days of sick leave/person-year
- Time between RA onset until 50% probability of being permanently work disabled varied from 4.5 to 22 years
- Health status related to work is an important priority for many patients

# Outcome of Aggressive treatment

- Clinical trials have shown that aggressive treatment in early RA leads to positive work-related outcomes
- Initial aggressive treatment with a combination of DMARDs relative to therapy with a single DMARD significantly reduced cumulative duration of sick leave and RA-related disability

# Diagnosis - Rheumatoid factor

- Immunoglobulin that binds to constant portion of IgG. Several Ig types – IgG, A, M
- IgM most easily identified.
- Nephelometry can detect all three .
- Positive assay  $\geq 20$  IU
- Present in 1-2% healthy individuals
- Present in up to 75% patients with RA
- Not very specific for RA relative to newer markers

# Anti-CCP antibodies

- Antibodies to citrullinated proteins (ACPA) are specific serological markers for rheumatoid arthritis (RA).
- RA-specific intracellular citrullinated proteins are present in synovium.
- As sensitive as RF in diagnosis of RA but more specific (95%)
- Titre of anti-CCP antibody reflects prognosis
- Anti-CCP antibodies in patients with RA are independently associated with the development of ischemic heart disease.

# Anti- MCV antibody

- Antibody to modified citrullinated vimentin antibody
- Anti-Sa antibodies detected in serum of 20-47% RA patients
- Highly specific
- Appear to identify subset of patients with prognosis for aggressive disease
- Sa antigen, a doublet of protein bands of about 50kDa has been found in synovium

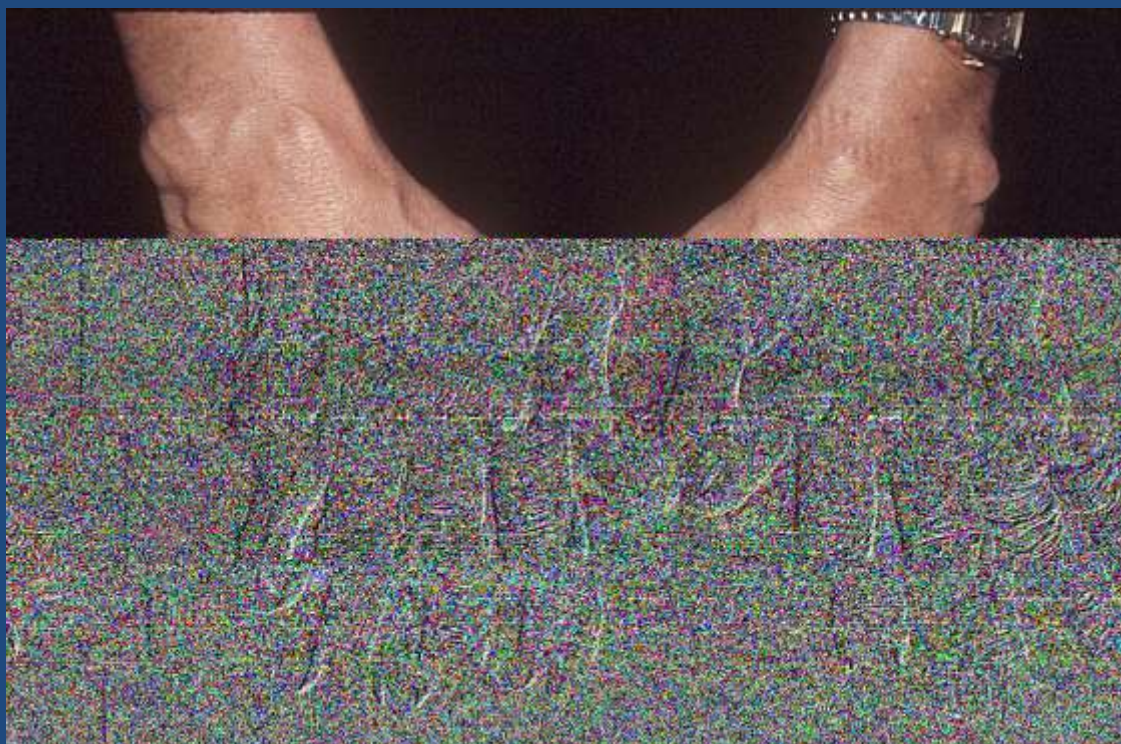
# Importance of Early Treatment: Damage

- RA patients have joint erosions early
  - ~40% within 6 months
  - ~60% within 1 year
  - >70% within 2 years
- Erosions represent permanent structural damage
- Joint damage may progress at rapid rate
- Prevention of damage with DMARD therapy early in disease can preserve patient function, prevent disability
- Much more aggressive approach to treatment
  - The earlier the better
  - Dose escalation/additional DMARDs if incomplete response
  - ‘Pyramid’ approach – completely outdated

# Goals of Therapy in RA

- Reduce pain and inflammation
- Improve physical function
- Retard/halt joint destruction
- Induce remission
- Improve survival

End-stage RA – now avoidable?



# RA – Symptomatic Treatment

- NSAIDs
  - Symptomatic relief, improved function
  - No change in disease progression
- Low-dose prednisone ( $\leq 10$  mg qd)
  - May substitute for NSAID
  - Used as ‘bridge therapy’
  - If used long-term, add Ca, Vit D, or bisphosphonates for osteoporosis risk
  - Possible disease modifying effect
- Intra-articular/parenteral steroids
  - For flares of symptoms

# DMARDs - General

- Disease modifying anti-rheumatic drugs
  - Improve symptoms, function and slow disease progression
  - ‘Steroid-sparing effect’
- Marked variability in response between pts
- High rate of discontinuation due to lack of efficacy and/or adverse effects
- Stopping DMARD may cause exacerbation
- Combination therapy often necessary
- Monitoring for toxicity necessary for most
- Risk/benefit ratio must be discussed with pts – NB issues of fertility/pregnancy

# Older DMARDs

- Minocycline [minocin]
  - Modest effect, may work best early
- Sulfasalazine [salazopyrin]
  - Moderate effect, low cost
  - Side effects – rashes, myelosuppression, GI, male infertility
- Hydroxychloroquine [plaquenil]
  - Mild disease, well tolerated, low risk ocular toxicity >5 yrs use
  - Not shown to prevent joint damage in RA, 1<sup>st</sup> line in mild lupus
- Intramuscular gold [myocrisin]
  - Slow onset, decreases progression, rare remission
  - Many AEs, requires close monitoring, rarely used
- Penicillamine [distamine]
  - Slow onset, many side effects, rarely used

# Older DMARDs

- Immunosuppressant/cytotoxic DMARDs
  - Azathioprine [imuran]
    - Slow onset, reasonably effective
    - Metabolite, mercaptopurine, can be used instead if GI intolerance to azathioprine
    - Thiopurine methyltransferase deficiency - ↑toxicity
  - Less frequently used
    - Cyclophosphamide
      - Effective for vasculitis, less so for arthritis
    - Cyclosporine [neoral, sandimmun]
      - Superior to placebo, renal toxicity

# Leflunomide

- Indications: RA, psoriatic arthritis, psoriasis
- Equal efficacy with MTX, can be used alone or with MTX
- Slowly absorbed, first-pass metabolism to active metabolite
- Half-life 16 days, 7-8 weeks to reach steady state in blood, loading dose can be given to hasten this (more GI side effects)
- Persists in body for up to 2 years
- Highly protein bound – may increase concentrations of diclofenac, ibuprofen but not warfarin, MTX

# Methotrexate

- First-line DMARD for RA
- Also used in a variety of other rheumatic diseases
- Symptomatic and functional improvement
- Slowing of joint damage
- Reduced mortality

# Biologic DMARDs

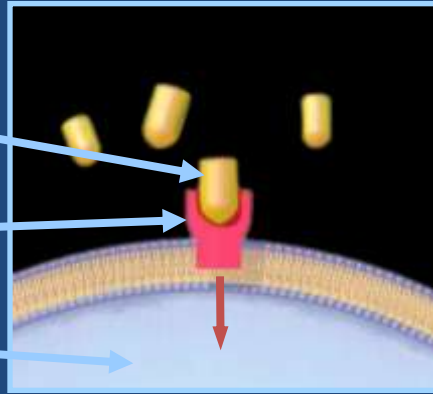
- Biologic cytokine antagonists inhibit the action of proinflammatory cytokines, T or B lymphocytes
- Include etanercept, infliximab, adalimumab (TNF) and anakinra (IL1), tocilizumab (IL-6), rituximab (B cells), abatacept (T cells).
- Development of anti-TNF therapies 'greatest advance in RA therapy since cortisone'
- Can induce remission – usually relapse if Rx stopped
- 'Targeted therapies' – target specific key components of the disease process
- Other therapies in development
- Other targets identified with increased understanding of the pathophysiology of autoimmune diseases

# Inhibition of Cytokines

Inflammatory cytokine

Cytokine receptor

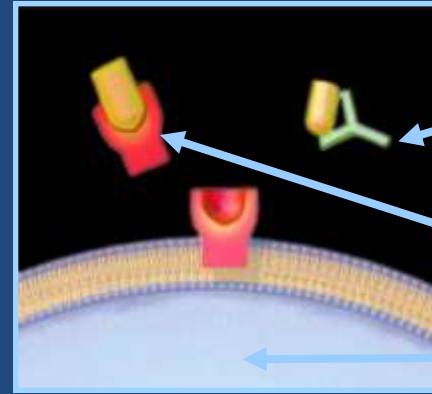
Inflammatory signal



Monoclonal antibody

Soluble receptor

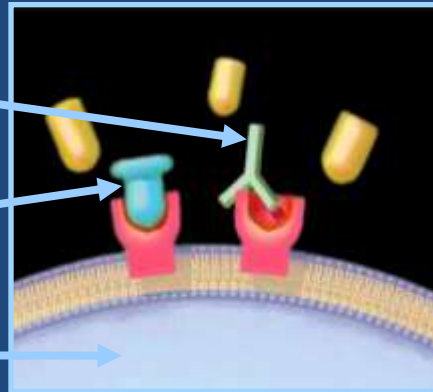
No signal



Monoclonal antibody

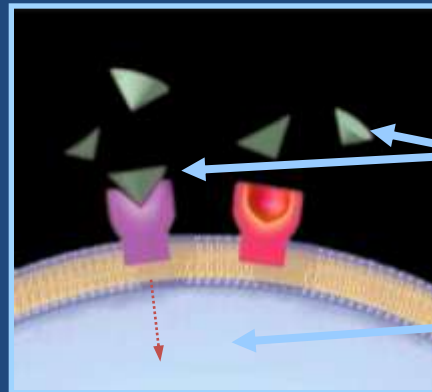
Receptor antagonist

No signal



Anti-inflammatory cytokine

Suppression of inflammatory cytokines



# Anakinra

- Can be used alone or in combination with other DMARDs (except TNF blocking agents)
- Modest effect vs anti-TNF therapy – reserved for patients who have failed all 3 anti-TNF agents
- Injection site reactions
  - 71% of patients (vs. 28% placebo)
  - Majority were mild
- Increased incidence of serious infections (bacterial, 2% vs. <1% placebo)
- Decrease in neutrophil counts has been observed-  
Recommend monitoring while on therapy

# Anakinra [Kineret]

- Recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist (additional methionine residue at amino terminus)
- Competitively inhibits naturally occurring IL-1 from binding to cells responsible for initiating inflammation and joint destruction
- Reduced PG, MMP production
- Reduced mononuclear cell infiltration
- Half-life of 4-6 hours
- Administer by sc injection daily

# Traditional DMARDs vs. TNF Antagonists

## Traditional DMARDs

- Improve signs and symptoms of RA
- Have slower onset of action
- Slow radiographic progression

## TNF Antagonists

- Improve signs and symptoms of RA
- Have rapid onset of action
- Inhibit radiographic progression

# TNF Antagonists

## Two Approaches

### Soluble Receptors

- Binds both TNF- $\alpha$  and TNF- $\beta$  (lymphotoxin)
- Moderate- to high-binding affinity for TNF- $\alpha$
- Half-life of 4-5 days
- Etanercept

### Monoclonal Antibodies

- High specificity; binds TNF- $\alpha$  only
- High binding affinity for TNF- $\alpha$
- Half-life of 8-14 days
- Infliximab, adalimumab

# Efficacy

- Anti-TNF treatment is associated with:
  - Inhibition of overall disease progression
    - decrease in joint erosions
    - improvement in joint space narrowing
  - Improvement in physical function compared with placebo
  - Rapid improvement in signs and symptoms
  - safe and well-tolerated in general
  - Durable effects > 4years

# Inflammatory arthritis which is not RA

- Anti-TNF therapies are effective in patients with spondyloarthropathies, psoriatic arthritis, sero-negative inflammatory arthritis
- Even in patients with advanced spinal ankylosis, greatly enhanced quality of life
- Evidence for reduction in inflammation-associated co-morbidities such as MI, CVA

# Potential Issues With Anti-TNFs

- Serious infections
  - Opportunistic infections including TB
- Malignancies, including lymphomas
- Congestive Heart Failure
- Demyelination
- Administration reactions
- Autoantibodies and lupus-like syndrome

# Anti-CD20 therapy- Rituximab

- B cell hyperreactivity and autoantibody production e.g SLE, RA
- CD20 is a membrane-associated glycoprotein that is highly expressed on surface of resting and activated mature B lymphocytes
- Role of CD20 poorly understood
- Treatment with CD20 antibody kills B cells
- Rituximab best explored antibody to CD20

# Rituximab (cont.)

- Initially used in cancer eg lymphoma
- Evidence for benefit in SLE, RA, Sjogrens
- Given in 'cycles' of two infusions 2x1000 mg Rituximab 2 weeks apart (100 mg methylprednisolone I/V cover)
- With or without MTX or other DMARDs

# Abatacept (T cell)

- Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) expressed on the surface of T cells.
- CTLA4 is the high avidity receptor for CD80 and CD86
- Engagement of CD80/CD86 provides essential costimulatory signals for T cell activation
- In absence of secondary signals, T cells become anergic when stimulated by antigenic peptides

# Abatacept (cont.)

- CTLA4Ig (abatacept) is a fusion protein consisting of the extracellular domain of human CTLA4 and a fragment of the Fc domain IgG1.
- First in new class of drug for RA known as co-stimulation blocker
- Abatacept administered as single 30 min infusion
- Inhibits T cell function but does not deplete T cells
- Significant clinical benefit in RA

# Tocilizumab

- Interleukin (IL)-6 receptor antagonist
- Humanised monoclonal antibody to IL6 receptor.
- Significant efficacy, few adverse events in controlled trials
- Given by monthly I/V infusion

# Effect of newer treatments of ability to work

- Early aggressive treatment of RA (e.g. with a combination of anti-TNF therapy and methotrexate) leads to significant attenuation of absenteeism among patients with early active RA as well as those with long-standing RA
- In practice, biologic therapies given after other DMARDs alone provide insufficient benefit
- Aim is for perfection/remission



# Barriers to use of newer agents

- Cost – roughly €10,000/patient per year for drug alone
- Screening and monitoring costs and time
- Education costs and time
- Currently, relatively accessible in Ireland compared with some other countries including UK

# Conclusion

- Recent drug development in the management of inflammatory arthritis has revolutionized outcomes
- Can expect rapid benefit (within weeks) in many in terms of reduction of pain, stiffness and increase in energy
- Some individuals may have difficulty with side effects, infections or have a history of malignancy

# Fibromyalgia and work

- Mean costs for absence from work and short-term disability in the FM and RA substantial and similar.
- Substantial cause of disability: risk factors middle age and previous heavy manual labour.
- Pain, fatigue and weakness most often claimed to affect ability to work
- Early intervention with patient-specific approach likely to be of greatest benefit

# Fibromyalgia

- Common cause of chronic musculoskeletal pain.
- Females aged 20 to 55 years.
- Inadequate treatment strategies to date.
- Only 25% responding to conventional treatment.

**TABLE 62.1 DIAGNOSTIC FEATURES  
OF FIBROMYALGIA**

**Cardinal features\***

Chronic, widespread pain  
Tender points on examination

**Characteristic features**

Fatigue  
Sleep disturbances  
Stiffness  
Paresthesias  
Headaches  
Irritable bowel syndrome  
Raynaud's-like symptoms  
Depression  
Anxiety

\*For classification criteria, patients must have pain for at least 3 months involving the upper and lower body, right and left sides, as well as axial skeleton, and pain in at least 11 of 18 tender points on digital examination.

**Table 1: Major characteristics of persons with fibromyalgia\***

Criterion	% Positive
Pain symptoms – widespread pain	97.6
Tenderness – 11 of 18 tender points	90.1

Depression	83.3	95.0
Anxiety	77.8	90.0
Insomnia	74.4	85.0
Stress	61.1	70.0
Head	52.2	60.0
PT	47.8	55.0
Interfering function	40.0	45.0
Neuroticism	33.3	35.0
Depression	30.0	30.0
High breast tenderness	28.9	30.0
PT impact	26.7	25.0
and a questionnaire	26.7	25.0

\*Data from the American College of Rheumatology 1990 criteria study

# Neurologic signs and Symptoms

- Blinded controlled study demonstrated neurologic physical findings in persons with FM
- Neurologic abnormalities include greater dysfunction in cranial nerves IX and X (42% vs 8%)
- More sensory (65% vs 25%), motor (33% vs 3%) and gait (28% vs 7%) abnormalities.
- Symptoms included photophobia (70% vs 6%), poor balance (63% vs 4%), weakness (58% vs 2%) and tingling (54% vs 4%) in arms or legs

# Cognitive dysfunction

- Many patients complain of concentration and memory deficits, 'fibrofog'
- Greater concurrence of 'fibrofog' with anxiety and depression
- Can have implications in occupations requiring high cognition/concentration

# Concept of Central Sensitivity Syndrome

- Common underlying pathophysiological mechanism in FM and related syndromes is CNS pain or sensory amplification
- Strong familial predisposition to CSS: studies clearly show that these somatic symptoms and syndromes are separable from depression and other psychiatric disorders
- A variety of biological stressors seem to be capable of either triggering or exacerbating these symptoms and illnesses

# Central Sensitivity Syndrome (cont.)

- Increased sensitivity to many stimuli other than pain (i.e., auditory, visual) suggesting a fundamental problem with pain or sensory processing rather than an abnormality confined to the specific body region where the pain is being experienced
- Concept that all individuals (with and without pain) have different “volume control” settings on their pain and sensory processing

# Central Sensitivity syndrome (cont.2)

- Other shared mechanisms, 1) neurogenic inflammation, especially of mucosal surfaces, leading to increased mast cells and the appearance of a mild inflammatory process; 2) dysfunction of the autonomic nervous system; and 3) hypo- thalamic pituitary dysfunction.
- Similar therapies are efficacious for all of these conditions, both pharmacological and non-pharmacological
- Do not respond to therapies that are effective when pain is due to damage or inflammation of tissues

# Clinical Syndromes Currently Considered Parts of the CSS Spectrum

- Fibromyalgia
- Chronic fatigue syndrome
- Irritable bowel syndrome and other functional gastrointestinal disorders
- Temporomandibular joint disorder
- Restless legs syndrome and periodic limb movements in sleep
- Idiopathic low back pain
- Multiple chemical sensitivity
- Primary dysmenorrhea

# Clinical Syndromes Currently Considered Parts of the CSS Spectrum (cont.)

- Headache (tension > migraine, mixed)
- Migraine
- Interstitial cystitis/chronic prostatitis/painful bladder syndrome
- Chronic pelvic pain and endometriosis
- Myofascial pain syndrome/regional soft tissue pain syndrome

**TABLE 62.2 SYNDROMES THAT OVERLAP WITH FIBROMYALGIA**

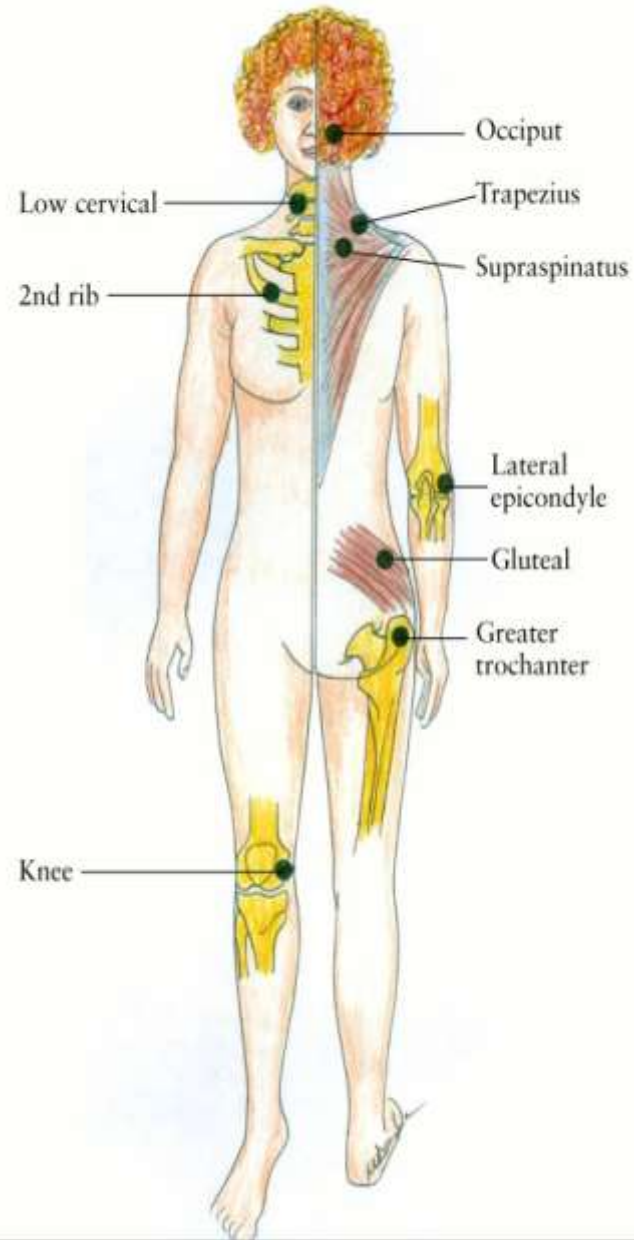
- Chronic fatigue syndrome
- Myofascial pain syndrome
- Irritable bowel syndrome
- Muscle, migraine headaches
- Irritable bladder, interstitial cystitis
- Gulf War syndrome

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**TABLE 62.4 DIFFERENTIAL DIAGNOSIS AND SYSTEMIC ILLNESSES THAT ARE ASSOCIATED WITH FIBROMYALGIA**

Condition	Helpful differential features	% with FM
Rheumatoid arthritis	Synovitis, serologic tests, increased erythrocyte sedimentation rate (ESR)	12
Systemic lupus erythematosus	Dermatitis, systemic vasculitis (renal, central nervous system, etc.)	22
Sjögren's syndrome	Lymphadenopathy, biopsy of salivary glands	11
Polymyalgia rheumatica	Increased ESR, elderly, response to steroids	?
Myositis	Increased muscle enzymes, weakness more than pain	?
Hypothyroidism	Abnormal thyroid function tests	?
Neuropathies	Clinical and electrophysiologic evidence of neuropathy	7

Figure 1



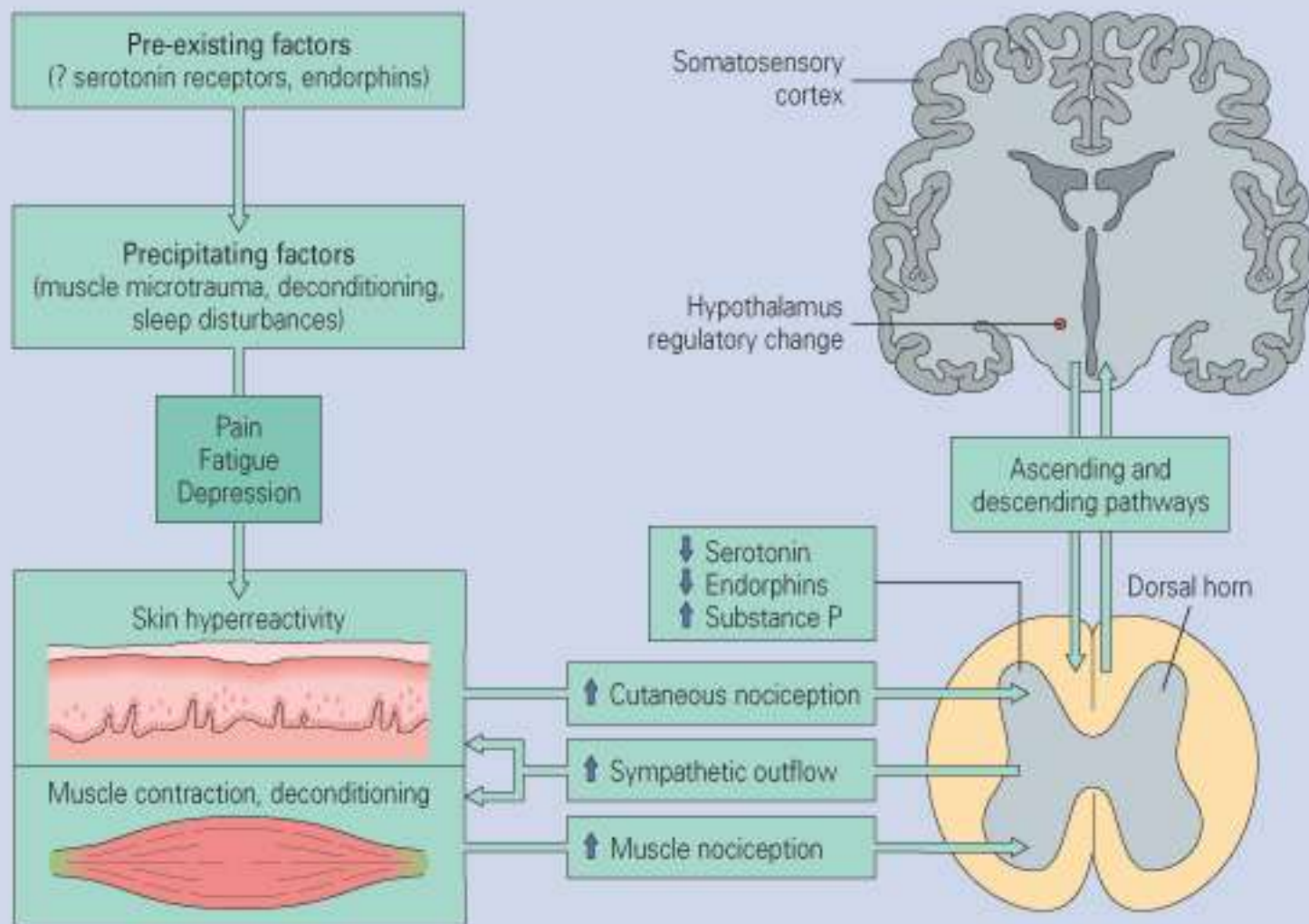
# Nocturnal factors intruding on sleep of rheumatic disease patients

- Alpha wave intrusion into delta wave sleep
- Bruxism
- Nocturnal myoclonus
- Musculoskeletal pain
- Emotional stress
- Systemic pain

**TABLE 62.6 MOST COMMON PRECIPITATING  
FACTORS IN FIBROMYALGIA**

Flu-like viral illness  
Usually unspecified  
Chronic fatigue syndrome  
HIV infection  
Lyme disease  
Physical trauma  
Emotional trauma  
Medications, especially steroid withdrawal

## A POSSIBLE PATHOPHYSIOLOGIC MODEL OF FIBROMYALGIA



# Management of Fibromyalgia

- Ultimate aim of treatment is for patients to become aerobically conditioned ('fit')
- Aerobic conditioning improves sleep quality
- Aerobic conditioning leads to endorphin production
- Increases energy/reduces fatigue

# Aerobic conditioning

- Exercise chosen should cause increase in heart rate associated with sweating
- Ideal forms include running, treadmill, exercise bike
- Brisk walking is an excellent way to start

# Therapeutic exercise

- Study of 84 minimally active adults with FM
- Randomized to 30 min moderate exercise 5-7 days/week vs education alone for 12 weeks
- Exercise group reported significantly less perceived functional deficits and pain
- No difference in fatigue, depression, BMI or tenderness

# Drug therapy in fibromyalgia

- Useful in short term to enable patient to start a program of aerobic conditioning
- Improve sleep quality
- Reduce pain

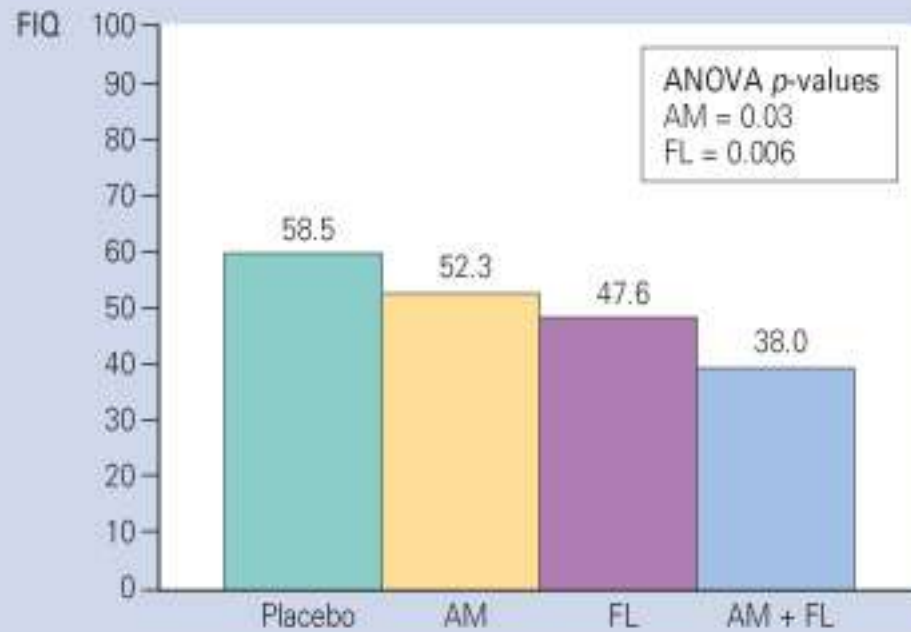
# Drugs useful in sleep disturbance

- Amitryptilene (10 - 50 mg)
- Nortryptilene (10-25 mg)
- Trimipramine (10-25 mg)
- Doxepin (10 mg)
- Molipaxin (50 mg)
- Gabapentin (100-300mg)
- Diphenhydramine (10 mg) or other sedating anti-histamines
- Pregabalin (75 mg)

# Use of SNRI/SSRIS

- Can reduce pain and stiffness in fibromyalgia
- Can increase energy
- Can relieve concurrent low mood
- Fluoxetine (SSRI) best studied
- Duloxetine (SNRI) more recently recognised and available
- Milnacipran (SNRI) not yet available

## COMBINATION TREATMENT WITH FLUOXETINE AND AMITRIPTYLINE



# Essential non-drug elements

- Exercise - aerobic conditioning
- Physiotherapy - neurostructural integration
- Diet
- Education
- Counselling
- Appropriate assistive devices and splints

# Background of Neurostructural Integration Therapy (NST)

- Novel soft tissue therapy
- Designed to relax muscles & fascia
- Specific & systematic manner
- No forceful manipulation
- Defined musculoskeletal points
- Resting periods

# Conclusions overall

- Fibromyalgia can be successfully managed in most cases
- Successful management requires more active input from patient than many other rheumatology conditions
- Aerobic conditioning ultimate aim
- Individualized approach with early intervention of greatest potential benefit