results of the CARDERA study, a 2-year randomized double-blind 2X2 factorial trial in early RA patients. Patients (n=467) were randomly assigned to 4 groups: methotrexate alone, methotrexate+cyclosporin, methotrexate+prednisone, and methotrexate+prednisone +cyclosporine. The target dose of methotrexate was 15 mg/week. Prednisone daily doses were tapered from 60 mg (weeks 1, 2) to 7.5 mg (weeks 7-28) to withdrawal (week 35). Cyclosporine was started 3 months after the start of methotrexate.

The number of patients with new erosions was reduced by ~50% by adding cyclosporine (p=0.01) or prednisolone (p=*0*.03); both treatments reduced in Larsen's X-ray scores by >2 units. Triple therapy also reduced disability and improved quality of life.

Dr. Choy concluded, "This study confirms the existence of a "window of opportunity" in early rheumatoid arthritis, when intensive combination therapy produces sustained benefits on damage and disability. Prednisolone and cyclosporin in combination with methotrexate reduce erosive damage independently; they act synergistically to improve physical function and quality of life."

Frank Buttgereit, MD, Charité University Hospital, Berlin, presented the results of a 3 month randomized, controlled phase 3 study which compared a newly developed modified-release (MR) prednisone tablet (designed to be taken at bedtime) which releases prednisone 4 hours after ingestion with immediate-release (IR) prednisone. The primary outcome measure was patient reported duration of morning stiffness.

A total of 288 RA (mean age 55.0 yrs, 14.2% male, mean disease duration 115.3 months) were randomly assigned to two groups. Treatment with MR prednisone resulted in a significant reduction in the duration of morning stiffness vs IR prednisone (22.7% vs 0.4%; p=0.0226). The study investigators concluded that MR prednisone provides a clinically relevant reduction of morning stiffness added to the known therapeutic effects of IR prednisone.

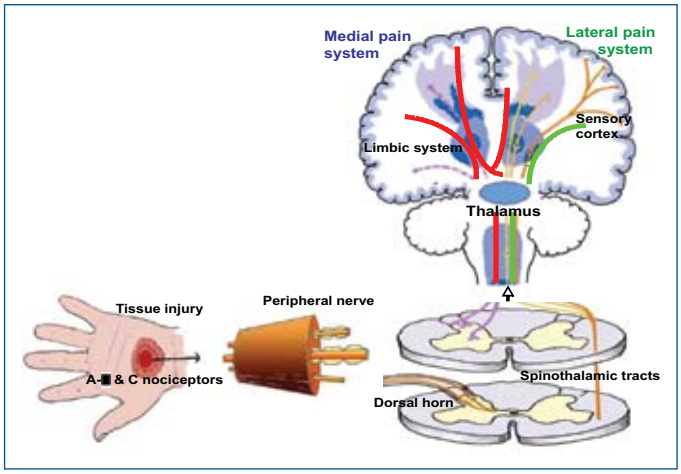
In summary, the magnitude and longevity of the effect of glucocorticoids on disease activity in RA is dependent on the daily dose, total dose, and dosing schedule. Beneficial effects on damage progression are apparent at low doses. These effects may be independent of the symptomatic effect, additive to that of other DMARDs, and may continue well after glucocorticoids are discontinued. Although the potential toxicity is considerable, in practice, it is similar to that of other antirheumatic agents (including NSAIDs).

New Insights into Managing Musculoskeletal Pain

Professor Anthony Jones, MD, University of Manchester, England, chaired an important session to provide new insights in managing musculoskeletal pain. Patients suffering from fibromyalgia perceive pain differently than healthy subjects, which may be the result of how pain is processed in the brain [Kulkarni et al. *Rheum* 2005]. State-of-the-art brain imaging techniques are being used to understand the processing of pain associated with fibromyalgia and chronic pain in general [Jones et al. *Brit Med Bull* 2003].

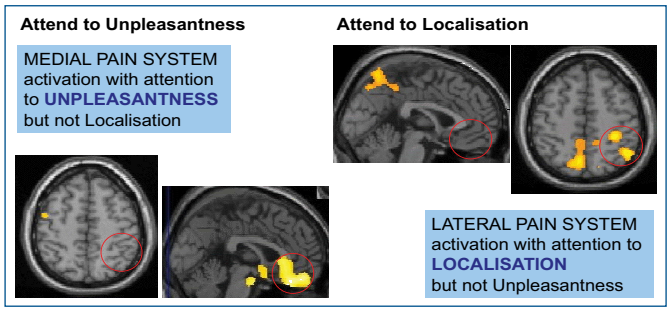
The part of the nervous system associated with pain as a consequence of organ or tissue damage is called the nociceptive system. The currently accepted theory is that there are two networks involved in pain processing in the brain: the lateral nociceptive system, which projects through lateral thalamic nuclei to brain regions including the primary and secondary somatosensory cortices; and the medial nociceptive system, which projects through medial thalamic nuclei to brain regions, including the prefrontal, insula and anterior cingulate cortices (Figure 1).

Figure 1: Pain Pathways.



The lateral pain system is thought to be responsible for the sensory aspects of pain such as its location. The medial pain system is thought to be responsible for the emotional aspects of pain, such as how unpleasant it feels. Both can be visualized with PET when activated [Kulkarni et al. *Eur J Neurosci* 2005]. Understanding the role of these brain areas in anticipation, attention, and emotional responses to pain is the next challenge (Figure 2).

Figure 2: Functions of the Medial and Lateral Pain Pathways.



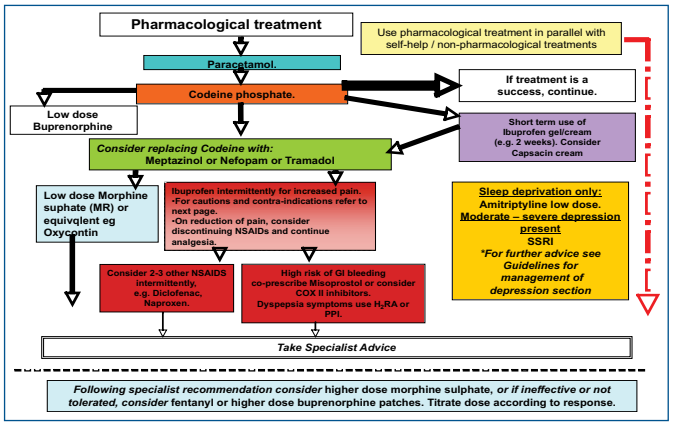
Chronic pain, however, may also be a result of damage to the nervous system itself, eg, pain after nerve injury, spinal cord injury pain, or post-stroke pain. This type of pain is called neuropathic pain, and occurs as a direct consequence of a lesion or disease affecting the somatosensory system. Nociceptive and neuropathic pain are both sensitive to treatment with opioids, but NSAIDs are more appropriate for nociceptive pain, whereas other substances (eg, anticonvulsants) are appropriate for neuropathic pain. Tricyclic antidepressants can be used as adjunct analgesics for most types of pain. Understanding the differential diagnosis of neuropathic vs nociceptive pain components guides therapeutic decisions in the treatment of chronic pain.

Opioids have an established role in the management of acute pain, pain associated with terminal illness, and as emerging clinical trial data suggests, in the management of persistent non-cancer pain. However, questions remain regarding the efficacy and safety of their use long-term. The risks of opioid treatment include failure to achieve analgesia, constipation, somnolence, dependence, tolerance, respiratory depression, and addiction.

The use of opioids for non-cancer pain (whether short- or long-term) has variable support from the clinical community. Some report failure of the key treatment goals: pain relief, improved quality of life, and improved functional capacity. Opioid use may be associated with reports of moderate/severe pain, poor self-rated health, unemployment, increased use of the healthcare system, and negative influences on quality of life [Eriksen J et al. *Pain* 2006]. However, other substantial trials have shown clear benefits [Rowbotham et al. *New Engl J Med* 2003].

When prescribing opioids for non-cancer pain, known risk factors such as abuse/misuse (eg, genetic, environmental factors, comorbid psychiatric diagnosis, previous history of substance misuse – including alcohol) should be identified and regular re-evaluations of drug efficacy, side effects, and pattern of opioid use should be performed. Treatment recommendations can be found at www.ampainsoc.org/advocacy/opioids.htm (Figure 3).

Figure 3: Treatment Options.



As mentioned in the discussion, the use of mild and stronger opiates in benign pain is very common. Many of these patients suffer from chronic recurrent acute pain, which does not neatly fit into chronic/acute pain categories. There is emerging evidence of cardiovascular risk of prescribing NSAIDS together with the established risks of gut damage, especially in the elderly. There is, therefore, a clear need for more substantial clinical trial data on the use of opiates in well psychologically defined clinical populations to properly assess the relative risks and benefits in these patients.

Monotherapy in Comparison to Patients with Concomitant DMARD Therapy

Kasia Owczarczyk, MD, University Hospital of Cologne, Germany, presented the results of a double-blind phase 2 trial which suggest that in patients with active rheumatoid arthritis (RA), despite methotrexate (MTX) treatment, a single course of two infusions of rituximab (alone or in combination with either cyclophosphamide or continued methotrexate) provided significant improvement in disease symptoms [Edwards JCW et al. *N Engl J Med* 2006]. Exact data depicting the degree of B-cell depletion, as well as the phenotype of residual B-cells in patients receiving rituximab monotherapy, in whom the use of standard DMARDs is precluded due to intolerance or inefficacy, is still lacking.

This study analyzed the kinetics of B-cell depletion and the phenotype of residual B-cells in 10 patients with