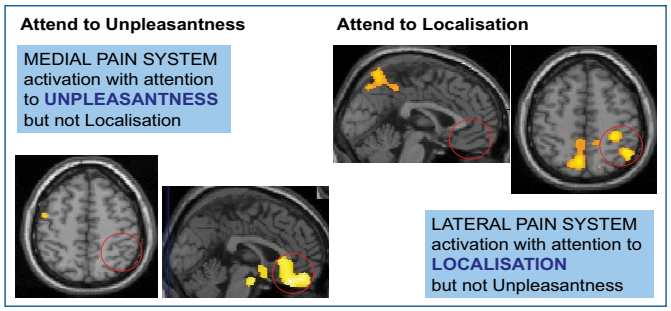
Figure 2: Functions of the Medial and Lateral Pain Pathways.



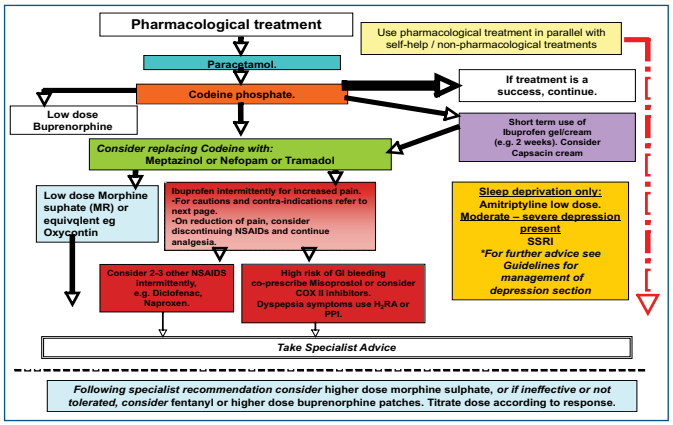
Chronic pain, however, may also be a result of damage to the nervous system itself, eg, pain after nerve injury, spinal cord injury pain, or post-stroke pain. This type of pain is called neuropathic pain, and occurs as a direct consequence of a lesion or disease affecting the somatosensory system. Nociceptive 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

active RA who were receiving rituximab monotherapy, as well as in 5 patients receiving a concomitant DMARD other than MTX (azathioprine, cyclosporine, leflunomide), and in 10 patients who received concurrent MTX therapy. All patients received 2g of rituximab (given as individual infusions) on days 1 and 15. CD19+ B-cell percentages were analyzed at baseline, on day 15, and at weeks 4, 8, 16, and 20. Absolute B-cell numbers were calculated based on WBC. Clinical response was analyzed using DAS28 and the EULAR response score.

This report presents preliminary data for 17 of the 25 patients who have completed a 4 month follow-up period after rituximab therapy.

Thirteen (13) patients achieved an effective B-cell deletion. Full depletion (<5 residual B-cell/ul) was achieved in 100% of patients in the rituximab monotherapy group; 2 of 3 patients receiving a DMARD other than MTX; and 6 of 8 patients receiving concomitant MTX therapy. The mean absolute CD19+ C-cell counts at the point of maximum deletion were similar in all groups.

When changes in the mean percentage of naïve (CD27-IgD+) and isotype-switched memory (CD27+ IgD-), double negative (CD27-IgD-), and plasma cells (CD20-$CD19^{low}$CD38+) were further analyzed, all subtypes of B-cells were depleted including cells with plasma cell precursor phenotype (mean ±SD 52.99±16.88).

Patients receiving rituximab monotherapy achieved a mean reduction in DAS28 of 1.67 (±SD 0.76) vs 1.84 (± SD 1.44) in the MTX group and 0.7 (± SD 0.29) in the alternate DMARD group. Good to moderate EULAR clinical response was achieved by 76% of patients receiving concomitant MTX vs 55% of those receiving an alternate DMARD and 60% in those receiving rituximab monotherapy.

In this study, rituximab induced a profound depletion of the peripheral B-cell pool when administered in combination with MTX or alternative DMARDs as well as in monotherapy. The degree of B-cell depletion did not vary significantly between study groups. In all subjects residual B-cells expressed predominantly an isotype-switched memory cells' phenotype.

Patients receiving rituximab monotherapy achieved similar clinical responses compared with those receiving concomitant DMARD therapy. However, long-term follow-up data on the efficacy of rituximab monotherapy is still lacking and further analysis will show whether B-cell re-population occurs earlier in this setting.

These data suggest that rituximab monotherapy can be used effectively in patients, who – for a variety of reasons – are unable to receive adjuvant DMARD therapy.

New Therapies for Gout

A key objective of long-term management of gout is "cure". This can be achieved by patient education, modification of the patient's risk factors (diet, obesity, hypertension, lipid levels), and by maintaining tissue urate levels below the saturation point for crystal formation (serum uric acid <360 μmol/l or 6 mg/dl) [Zhang W et al. *Ann Rheum Dis* 2006].

The purine xanthine oxidase inhibitor allopurinol is the most widely used urate-lowering therapy (ULT) and offers a wide-dose range for individual dose titration. Allopurinol administered 100-900 mg daily inhibits xanthine oxidase, and thus uric acid formation. Its principal drawback is allopurinol "hypersensitivity" syndrome which is more common in patients with renal impairment. Although rare, it can prove fatal.

Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase, is a potential alternative to allopurinol for patients with hyperuricemia and gout. At a daily dose of 80 or 120 mg, febuxostat was more effective than a standard fixed dose of allopurinol (300 mg/day) in lowering serum urate after 1 year (Becker MA et al. *N Engl J Med* 2005). Febuxostat is awaiting regulatory clearance in Europe. Because of its efficiency at the doses that will be available (80mg and 120mg), prophylaxis of acute attacks is recommended when initiating therapy.

Uricosurics (sulphinpyrazone, probenecid, benzbromarone) have limited availability and are contraindicated, and less effective, in patients with renal impairment. Uricosurics predominantly act on urate transporter 1 (URAT-1) in the proximal renal tubule. Benzbromarone is a very efficient urate lowering agent, even in patients with mild-moderate renal impairment, but because of rare hepatotoxicity its use has been restricted. Therefore, other ULTs are being examined. Losartan and fenofibrate cause modest reductions in serum uric acid (20-40%) via a uricosuric effect and can be adjunctive agents in gout patients that require treatment for hypertension or lipid reduction [Bardin T. *Ann Rheum Dis* 2003]. Supplementation with 500mg ascorbate/day can reduce serum uric acid in hyperuricaemic patients by close to 20% [Huang H-Y et al. *Arthritis Rheum* 2005], again through a uricosuric effect.