The latest advance in NSAID research is the development of selective cyclo-oxygenase type 2 (COX-2) inhibitors. The COX-2 isoenzyme is thought to be responsible for prostaglandin production at sites of inflammation. Selective inhibition of the COX-2 isozyme seems to have anti-inflammatory and analgesic actions without gastrointestinal toxicity, but the clinical relevance of this remains to be determined.[9]

Topical NSAIDs may also be useful in the short-term management of acute low back pain, but are more expensive than oral preparations. Plasma NSAID concentrations are considerably lower after topical compared with oral administration, thus minimising systemic adverse effects.[10] However, such adverse effects have been reported after topical NSAIDs. The use of oral NSAIDs in conjunction with topical NSAIDs available over-the-counter should be discouraged.

Muscle relaxants/anxiolytics

Painful muscle spasm is sometimes associated with acute low back pain, and a muscle relaxant such as carisoprodol or orphenadrine citrate† in combination with an analgesic can give symptomatic relief.[1,3] These agents can be associated with behavioural alterations including sedation and paradoxical agitation; they also have some potential for abuse.[1]

Diazepam and other benzodiazepines have muscle relaxant properties, and may be particularly useful for short-term treatment when a definite anxiety state is a significant factor in low back pain.[3,6] It should be given in the lowest dose for the shortest time.[3] Benzodiazepine therapy for a maximum of 1 week may also be useful in patients who have difficulty sleeping because of back pain.[4]

Antidepressants

Antidepressants can elevate mood and may increase pain tolerance in depressed patients with chronic low back pain. Amitriptyline is more effective than other antidepressants for relieving back pain, but causes more adverse effects such as dry mouth, constipation and drowsiness.[3]

A typical dosage regimen for amitriptyline would be 10 to 25mg at night, gradually increasing up to 100 to 150mg until benefits are achieved or adverse effects occur. The onset of analgesia may take up to 3 months.[3]

Corticosteroids

There is little evidence to support the use of local or epidural injections of corticosteroids to relieve lower back pain.[3,4] Corticosteroids should not be used in patients with back pain due to osteoporosis, since they may increase bone loss.[3]

Other therapies

Bedrest is important in the initial management of low back pain.[1,4,11] However, too much bedrest is counterproductive. Two days in bed is as good as 2 weeks.[3] In the recovery period, it is better to mobilise and experience some back pain, than risk the complications of bedrest and the sedating effects of too many drugs.[3]

Other therapeutic interventions that may be of use in the management of low back pain include specific exercises, manual therapy and manipulation, corsets, transcutaneous electrical nerve stimulation, and physiotherapy.[1,4,11]

† Orphenadrine citrate has been withdrawn from the Spanish market; amphotericin B and pentamidine are not available in Denmark.

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Leishmaniasis: pentavalent antimonials still primary therapy

Pentavalent antimonials remain the primary therapy for all forms of leishmaniasis, despite a plethora of alternative agents having been investigated. However, amphotericin B† and pentamidine† appear to be suitable options in antimonial-refractory disease, and have been evaluated as first-line options also. Amphotericin B may become the more attractive option as experience with the better-tolerated liposomal formulations accumulates. In addition, oral agents such as the azole antifungals and allopurinol have shown promise.

Another novel approach is to modulate the immune system in order to prevent or treat the infection.

Leishmaniasis

Leishmaniasis is caused by various protozoa of the genus *Leishmania*, with the manifestations of the disease differing according to the species of parasite involved (see table 1). The infection is transmitted to humans from animals such as rodents and dogs following sandfly bites.

This disease is endemic to many tropical and subtropical countries, including those in Central and South America, Africa and the Middle East. Travellers to endemic regions may return to their country of residence with the infection. For example, some US military personnel acquired the infection during postings in the Middle East.[1] In addition, it appears that the disease has been acquired in Texas, US.[1]

Leishmaniasis is also emerging as an important infection among immunocompromised patients, and visceral disease is now common among HIV-infected patients in Mediterranean countries.[5]

Thus, physicians the world over should maintain an index of suspicion for leishmaniasis, particularly among patients who have visited endemic regions in the last 2

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Table 1. Characteristics of *Leishmania* infection[1-4]

Form of disease	Disease characteristics	*Leishmania* species
Old World cutaneous (Oriental sore)	Papules/nodules at site of inoculation enlarge and then ulcerate Depending on the species of parasite, there may be single or multiple lesions that heal spontaneously within a year or in up to 3 years Rarely forms chronic, nonhealing sores	*L. major, L. tropica, L. aethiopica, L. infantum*
New World cutaneous (Oriental sore, Chiclero's ulcer)	As above, although Chiclero's ulcer may persist for up to 20 years Chiclero's ulcer of the ear may cause destruction of the pinna May heal spontaneously, but tends to be more severe and long-lasting than Old World forms	*L. mexicana* (and subspecies including *mexicana, amazonensis*), *L. braziliensis* (and subspecies including *panamensis* and *guyanensis*)
Diffuse cutaneous	Widely disseminated plaques, papules and nodules, especially on the face and limbs, without mucosal involvement or ulceration Does not heal spontaneously	Old World: *L. aethiopica* New World: *L. mexicana* (and subspecies including *mexicana, amazonensis, pifanoi, garnhami* and *venezuelensis*)
Mucocutaneous (Espundia)	Cutaneous disease does not heal, and there is spread to the mucosa, particularly the nasal mucosa, where soft tissue and cartilage is progressively destroyed Disfiguring disease, with secondary bacterial infections and pharyngeal obstruction Does not heal spontaneously, and may be fatal	New World: *L. braziliensis* (and subspecies including *panamensis* and *guyanensis*) Old World *Leishmania* spp. are not associated with this form of disease
Visceral (Kala-azar)	Gradual onset of systemic disease Signs/symptoms include hepatomegaly, splenomegaly, anaemia, pancytopenia, anorexia, bodyweight loss, fever, shivering, malaise, darkening of the skin of the face, hands and feet Bleeding and infectious complications may be fatal Does not heal spontaneously	Old World: *L. donovani* (including subspecies *donovani, infantum*) New World: *L. d. chagasi*

years and whose lesions have failed to respond to other therapies.[1]

Identification of the parasite is an important step when planning therapy, since the various *Leishmania* spp. differ in their response to treatment.[1] This should also be borne in mind when reviewing the available clinical data. Notably, Old World cutaneous leishmaniasis generally heals spontaneously, and it has been suggested that this type of disease should be managed conservatively, either by allowing spontaneous healing to occur or using local therapy.[1]

Therapy

Pentavalent antimonials

Pentavalent antimonial compounds such as meglumine antimonate† and sodium stibogluconate† have been the mainstay of leishmaniasis therapy for decades.[4]

These compounds may be injected intralesionally for mild, early Old World cutaneous leishmaniasis. However, pentavalent antimonials must be administered by intramuscular (IM) or intravenous (IV) injection in more severe disease, which limits their usefulness in rural settings in undeveloped countries where the disease is rife.[1]

The dosage of pentavalent antimonials currently recommended by the US Centers for Disease Control is 20 mg/kg/day, and the recommended duration of therapy is 20 days in cutaneous disease and 28 days in mucocutaneous or visceral disease.[6]

In the majority of forms of leishmaniasis (both Old and New World), systemic pentavalent antimonials are associated with cure rates of between 60 and 90%.[1,3]

However, *L. aethiopica* infections do not generally respond to pentavalent antimonials.[4] Thus, it is recommended that cutaneous disease caused by this parasite is left to heal spontaneously, while oronasal lesions or diffuse cutaneous disease require treatment with an alternative agent such as pentamidine.[4]

In addition, there has been an increase in antimonial-resistant disease throughout the world, particularly in East Africa and India, and the need for alternatives to antimonials is becoming more acute.[3,7,8]

Moreover, there is concern regarding the tolerability of these agents. The most common adverse effects associated with pentavalent antimonials include anorexia, nausea, vomiting, malaise, myalgia, arthralgia and headache.[4] Rarely, severe renal, hepatic or cardiac events may occur, but the pentavalent agents are generally better tolerated than trivalent antimonials.[4]

Alternative parenteral agents

Pentamidine and amphotericin B have been recommended as second-line agents in patients who do not respond to, or relapse following, therapy with a pentavalent antimonial.[2,4] However, both of these agents must be administered parenterally, and may be associated with significant adverse effects such as renal impairment.

In one trial in patients with New World cutaneous leishmaniasis, IM pentamidine 2 mg/kg every other day for 14 days had comparable efficacy to IM meglumine antimonate equivalent to 20 mg/kg/day of elemental anti-

† Meglumine antimonate is not available in Denmark, Germany, The Netherlands or the UK and may be prescribed through the special access scheme in Australia; sodium stibogluconate is not available in Denmark, Germany or The Netherlands, is available from the Department of Foreign Drugs in Spain, may be obtained only through an importation procedure in France, has emergency release status in Canada, and may be prescribed through the special access scheme in Australia; in the US, sodium stibogluconate may be obtained from the Centers for Disease Control on an Investigational New Drug basis for treatment of specific patients with leishmaniasis, and so long as the physician agrees to register as a Clinical Investigator.

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mony for 20 days (both produced cure in >90% of patients).[9] Untreated patients in this trial had a cure rate of <36%. Overall, adverse events were more frequent in meglumine antimonate than pentamidine recipients (39 *vs* 30%, respectively) but fewer meglumine antimonate recipients withdrew because of adverse events (4 *vs* 15%).

IV amphotericin B 0.5 mg/kg on alternate days for 28 days has been compared with IM sodium stibogluconate 20 mg/kg/day for 40 days as first-line treatment of visceral leishmaniasis in India.[10] 100% of amphotericin B recipients and 70% of sodium stibogluconate recipients had resolution of signs and symptoms, and negative bone marrow smears, after 6 weeks ($p<0.001$).

IM pentamidine 4 mg/kg on alternate days (20 doses) and IV amphotericin B 0.5 mg/kg on alternate days (14 doses) have been compared in a trial involving 120 patients with visceral leishmaniasis that had not responded to therapy with antimonials.[11] Amphotericin B produced significantly more cures at 6 weeks (100 *vs* 80%) and faster resolution of fever (6 *vs* 8 days) than pentamidine.

The development of liposomal formulations of amphotericin B may improve the risk-benefit ratio for the drug, by improving tolerability.[12] Liposomal amphotericin B has been evaluated in visceral leishmaniasis in patients in Brazil and the Mediterranean.[13,14] In these uncontrolled studies, all immunocompetent patients were cured following 7 to 10 days' treatment with liposomal amphotericin B. Therapy was less successful in immunocompromised patients.[14] Notably, liposomal amphotericin B was generally well tolerated in these studies, and was not associated with either renal or hepatic toxicity.

Promising oral agents

Oral agents are desirable for the treatment of leishmaniasis, since they would facilitate outpatient therapy and avoid many of the costs and inconveniences associated with parenteral administration.

Oral azole drugs such as ketoconazole and itraconazole have been evaluated in both visceral and cutaneous leishmaniasis, with mixed results.

Two reports of small, uncontrolled studies of visceral leishmaniasis in India described cure rates of approximately 80% following treatment with ketoconazole 600 mg/day for 4 weeks, even among patients with antimony-resistant disease.[15,16] However, a third report from India described complete lack of response to ketoconazole 400 to 800 mg/day among 6 patients with antimony-resistant visceral leishmaniasis.[17]

Trials conducted with azole antifungals in cutaneous leishmaniasis underline the importance of the species of protozoan. A trial in Guatemala showed that ketoconazole was more effective than sodium stibogluconate among patients with *L. braziliensis* infection, while the reverse was true for *L. mexicana* infection.[18] Among patients with *L. b. panamensis* cutaneous leishmaniasis, oral ketoconazole was comparable in efficacy to IM sodium stibogluconate.[19] Another study reported that itraconazole was no more effective than placebo in patients with cutaneous disease caused by *L. aethiopica*.[20]

In other trials, where the species of parasite causing cutaneous leishmaniasis was not identified, itraconazole produced promising results in Kuwait[21] and India.[22] However, a controlled trial indicated that itraconazole was no better than placebo, and was significantly less effective than either pentamidine or sodium stibogluconate, in patients with New World cutaneous leishmaniasis.[9]

Allopurinol has been evaluated in leishmaniasis, in an attempt to exploit the unusual purine metabolism of the protozoan.[23] In a controlled trial, oral allopurinol 20 mg/kg/day for 15 days was associated with a significantly higher cure rate than parenteral meglumine antimonate equivalent to 20 mg/kg/day elemental antimony for 15 days among patients with cutaneous disease caused by *L. b. panamensis* (80 *vs* 36%).[24] Combining the two drugs yielded a response rate comparable to that attained with allopurinol alone (74%). These results require confirmation before they are extrapolated to other settings, however.[7]

A smaller trial, involving 18 Panamanian patients with mild cutaneous disease, indicated that allopurinol riboside had modest efficacy.[25] Cure was observed in 3 of 9 patients receiving allopurinol riboside 1250mg 4 times daily for 28 days. Combined therapy with allopurinol and probenecid 500 mg 4 times daily was also associated with a relatively low response rate (56%) in this trial.[25]

In visceral leishmaniasis, combination of allopurinol with pentavalent antimonials has yielded encouraging results among children infected by either *L. donovani*[26] or *L. infantum*,[27] and in patients with concomitant HIV infection (provided that treatment duration was ≥6 weeks).[28]

Immunotherapeutic approaches

It has been observed that the different forms of leishmaniasis are associated with varying immunological responses.[3] Visceral and diffuse cutaneous leishmaniasis do not induce a cell-mediated immune response, in contrast to cutaneous and mucocutaneous leishmaniasis in which such responses are observed.[3] Importantly, it appears that T cells from patients with visceral and diffuse cutaneous disease do not produce interferon-γ, a cytokine known to enhance the antileishmanial activity of macrophages.[29]

Augmentation of pentavalent antimonial therapy with interferon-γ has produced very encouraging results in difficult-to-treat patients with either severe visceral leishmaniasis, or visceral disease that had been refractory to previous treatment.[3] Overall cure rates of 100 and 59%, respectively, were obtained in these patients and the investigators stated that *'these results are the best reported for such difficult cases'*.[3]

Vaccine development is also underway. Approaches that have been used include killed parasites (administered with or without BCG), fractionated antigens and a *Leishmania* gene inserted into recombinant BCG.

One of these vaccines, administered for the treatment of patients with localised cutaneous leishmaniasis, achieved similar efficacy to, and better tolerability than, meglumine antimonate in one trial.[30]

Two other studies have demonstrated that leishmaniasis vaccines are immunogenic and have potential as prophylaxis of cutaneous leishmaniasis,[29,31] but further research is required before vaccination becomes a viable option in endemic areas.

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Is capitation funding the way forward for mental health provision?

Capitation financing appears to offer advantages over fee-for-service funding arrangements for patients with severe mental illness.[1]

However, to be successful, it appears that such programmes must be specifically tailored to patients with chronic illness, be managed flexibly and creatively and with input from patients and their families, and incorporate adequate quality assurance measures.[1]

While capitation systems must be implemented carefully and are not without problems, the potential benefits for patients with chronic mental illness appear to be great. Typically, these patients have been ill-served by private and public healthcare insurance providing reimbursement on a fee-for-service basis, as is exemplified by the US situation. A report published in 1993 by the US National Advisory Mental Health Council noted that, among patients with employer-based private insurance coverage:

- hospital coverage was more restrictive for mental illness than other types of illness in over three-quarters of cases
- for approximately one-half of patients, coverage for hospitalisation for mental illness was ≤50% of that for physical illness
- more than one-third of patients had an additional or separate lower maximum value on annual expenses relating to mental health
- outpatient coverage for mental health services was restricted in 95% of insurance plans.[2]

Public, federally funded insurance programmes in the US, such as Medicaid and Medicare, also restrict treatment for mental disorders to a greater extent than treatment for other disorders.[2]

In the same report, it was estimated that the cost of undertreatment of severely ill patients with mental illnesses currently exceeds the expenditure required to provide coverage commensurate with that provided for other disorders. Notably, it was calculated that savings of $US2.2 billion annually would accrue from the provision of commensurate coverage.[2] The savings would be due to reductions in morbidity and mortality, criminal justice system costs, social welfare costs, incarceration costs and general medical costs.

Capitation in theory

Capitation involves the prospective payment of a fixed sum of money per patient for a defined unit of time (e.g. annually) to a healthcare provider who then undertakes to ensure that the individual receives appropriate care.[1] Capitation has both potential advantages and disadvantages for the patient, insurer and healthcare provider (see table 1).

Capitation in practice

There have been several trials of capitated payment systems among patients with mental illness, and at least 20 US states have considered capitation as a means of controlling medical expenses among the indigent population.

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