Pharmacotherapy of multiple sclerosis: current status

RICHARD A. RUDICK, MD; DONALD E. GOODKIN, MD; RICHARD M. RANSOHOFF, MD

■ Pharmacotherapy plays an important part in the overall management of patients with multiple sclerosis. Most therapies directed at altering the natural history of the underlying disease process are only partially effective or are controversial or experimental. However, many effective symptomatic therapies are available to the clinician. The action and uses of corticosteroids in multiple sclerosis are discussed, and approaches to the treatment of spasticity, paroxysmal disorders, bladder dysfunction, cerebellar ataxia, neurobehavioral manifestations, fatigue, and acute and chronic pain in patients with multiple sclerosis are examined.
□ INDEX TERMS: MULTIPLE SCLEROSIS; AZATHIOPRINE; POLYMERS; CYCLOPHOSPHAMIDE; CYCLOSPORINS; INTERFERONS; PLASMAPHERESIS; LYMPHATIC IRRADIATION □ CLEVE CLIN J MED 1992; 59:267–277

COMPREHENSIVE CARE for patients with multiple sclerosis (MS) extends beyond neurologic diagnosis and pharmacotherapy. Patients also need support and information over time, including physical and occupational therapy, psychological assessment and intervention, help with social services, and attention to family, vocational, and insurance concerns. The complex problems encountered by some MS patients require a multidisciplinary approach.

In this context, pharmacotherapy plays an important role in overall patient management. In a previous article,[1] we reviewed clinical trials of experimental therapeutic agents in MS. While most therapies directed at altering the natural history of the underlying disease process are only partially effective or are controversial or experimental, many effective symptomatic therapies are available to the clinician. This article summarizes approaches used in the daily care of symptomatic problems experienced by MS patients.

CORTICOSTEROID THERAPY

Mechanisms of action

Corticotrophin and steroids are the most widely used medications for treating symptomatic exacerbations in MS patients. Judicious use of these drugs can hasten improvement of functional impairment associated with exacerbations. Three possible mechanisms may explain the observed benefits of these medications:

First, corticosteroids reduce inflammation and edema. It has been hypothesized that edema disrupts neuronal conduction, resulting in temporary deficits

From the Mellen Center for Multiple Sclerosis Treatment and Research, Department of Neurology (R.A.R.,D.E.G.,R.M.R.), and the Department of Molecular Biology (R.M.R.), The Cleveland Clinic Foundation.
Address reprint requests to R.A.R., Mellen Center, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

which are evident either on neurologic examination or during evoked-response testing. Evidence suggests that plaque edema, as measured by computed tomography (CT) of the brain, is reduced more effectively by administering steroids at high doses (1.5 g methylprednisolone [MP] intravenously [IV]) rather than at low doses.[2,3] However, no correlation has been shown between clinical status and breakdown of the blood-brain barrier as evident by CT scan.

Second, metabolic or physiologic effects may underlie the benefits of corticosteroids. The physiologic effects of corticosteroids on neural tissue are poorly understood and may be due in part to altered electrolyte concentrations within the central nervous system (CNS). In addition, corticosteroids may reduce the concentration of complement components that mediate partially reversible neuroelectric blocking effects,[4] although consistent improvement in nerve conduction velocity in patients treated with corticosteroids has not yet been demonstrated.[5]

Third, corticosteroids may have important immunologic effects. Intrathecal immunoglobulin G (IgG) synthesis is elevated in 90% of MS patients.[6] Many corticosteroid preparations can reduce cerebrospinal fluid IgG synthesis in MS patients. It appears that MP more significantly reduces intrathecal IgG synthesis than other steroid preparations, and that high doses (eg, 15 mg/kg/day) are more effective than low doses. The clinical significance of this effect is uncertain, since no consistent relationship has been demonstrated between intrathecal IgG synthesis and the clinical course of MS.

The effects of adrenocorticotropic hormone (ACTH) on intrathecal IgG synthesis are conflicting, possibly because of adrenal hyporesponsivity to ACTH in MS patients.[7,8] High doses of MP have also been reported to reduce the intensity of cerebrospinal fluid oligoclonal bands.[9] ACTH gel, 100 units intramuscularly (IM) for 10 days, was reported to decrease the number of cerebrospinal fluid lymphocytes.[10] MP resulted in increased CD8 cells in MS patients,[11] a finding of potential importance, since the percentage of suppressor lymphocytes was reported to fluctuate with disease activity in MS.[12] One or more of these mechanisms may explain the short-term beneficial effects of corticotrophin and corticosteroids in MS patients, which will be reviewed further below.

Acute exacerbations

The widespread use of steroids for MS exacerbations was encouraged by results of the Cooperative Study in the Evaluation of Treatment with Corticotrophin in MS.[13] Centers participating in that study used standardized methods of patient evaluation and data collection. Patients were randomized to receive ACTH gel (40 units IM bid for 7 days, 20 units IM bid for 4 days, and 20 units IM qd for 3 days) or matched placebo within 8 weeks of a documented exacerbation. Patients and examining physicians were blinded to the treatment arm. The patients were hospitalized and examined within 24 hours of initiating treatment, again on days 7 and 14 during therapy, and finally on days 7 and 14 after completing therapy. A total of 103 patients were treated with ACTH and 94 with placebo. The treatment groups were well matched for demographic and disability markers. The blind was judged to be adequate. More ACTH-treated patients exhibited improved Kurtzke Disability Status scores at the end of the 2-week treatment period (58% vs 38%) and at the final study visit 2 weeks later (65% vs 47%). The duration of these benefits was not determined, since the patients were only followed for 4 weeks. Nevertheless, this study has had a profound effect on the way neurologists treat MS exacerbations.

The value of corticotrophin compared with one or another corticosteroid remains unclear. Recent evidence suggests that high-dose pulses of intravenous MP may have a more rapid onset of action and may be more effective than corticotrophin or other steroid preparations. Dowling reported rapid improvement in five of seven relapsing-remitting MS patients treated with MP (600 mg IV daily for 3 days followed by oral prednisone tapered slowly over 90 to 120 days).[14] Durelli and associates compared MP to placebo (15 mg/kg/day for 3 days followed by oral prednisone 100 mg/day tapered over 120 days) in patients who had been in relapse for fewer than 8 weeks and had shown no spontaneous improvement.[9] Clinical improvement was found to be significantly more frequent and the duration of relapse significantly shorter in 13 MP-treated patients compared with 10 placebo-treated controls. Barnes[15] compared the clinical effect of ACTH (80, 60, 40, and 20 units IM for 7 days) and MP (1 g IV qd for 7 days) in patients with acute relapse. Initial improvement at 3 and 28 days was more significant in the MP-treated group but was no longer evident at 3 months. Milligan[16] compared MP (500 mg/day IV for 5 days) with saline placebo in relapsing patients within 8 weeks of exacerbation. Significantly lower disability scores were seen in the MP-treated patients at 1 and 4 weeks, but no later follow-ups were reported. The same protocol was administered to

chronic-progressive patients, and lessened spasticity was seen at 4 weeks in the MP-treated patients.[4] No other improvement was seen in the chronic-progressive patients, and data obtained 13 to 35 months later showed no difference in disability between the MP and placebo-treated groups.

Many clinicians now use MP in preference to ACTH, in part because of the aggregate evidence in the above studies. Support for this choice comes from data showing reduced plaque edema on CT scans with high but not low doses of corticosteroid, and from the observed effects on cerebrospinal fluid IgG and intrathecal IgG synthesis.

Long-term steroid use

Though steroids are widely used to manage acute attacks in MS patients, their role in the long-term management of MS has not been rigorously investigated. It has been stated that chronic daily use of corticosteroids does not significantly slow progression of disability.[17] In 1961, Miller[18] compared prednisolone (10 to 15 mg/day po), aspirin (6 g/day po), and placebo in 86 MS patients followed for 18 months. The trial was randomized and patients were reasonably matched for disability, age, course, and disease duration. No difference was seen between treatment groups by then-accepted measures of disability, exacerbation rate, or patient self-assessment at 6 or 18 months. In 1967, Millar[19] reported the results of long-term treatment of MS with corticotrophin. In this randomized, controlled, but unblinded study, 181 patients were treated with ACTH (15 to 25 units IM qd; dose was adjusted according to "facial mooning just evident") and compared with 169 patients who were treated with placebo. Patients were examined each 3 months for 16 to 23 months. The authors found no benefits in the ACTH-treated group.

Thus, data at present do not support chronic use of ACTH or oral prednisone. However, no studies have addressed the potential value of intermittent pulses of high-dose intravenous MP. This would be an important investigation, given the short-term benefits consistently observed with brief pulses of MP and its relatively limited toxicity. A trial investigating the role of high-dose vs low-dose pulses of MP in relapsing MS is in progress at the Mellen Center of The Cleveland Clinic Foundation.

Practical steroid therapy

The clinician should avoid injudicious use of steroids: their use should be restricted to patients with exacerbations of functional significance, such as the onset of paraparesis, loss of manual dexterity, or obvious visual deterioration. The use of steroids for symptom fluctuations without functional consequence, even if an important source of concern to the patient, should be avoided. Most experienced clinicians and patients have noted that the effects of steroids are transient and diminish with repeated use, so that a patient may eventually reach a stage of steroid-unresponsiveness. It is not clear whether restricting the use of steroids can delay or prevent steroid-unresponsiveness, but this approach would seem prudent at present.

For significant exacerbations, one can choose to administer oral prednisone or intravenous MP. Oral steroid administration is easier to accomplish for practical reasons. Prednisone 60 mg is administered in a single morning dose for 7 days, followed by tapering of the drug over the next 7 days. During the first week, it is advisable for the patient to report his condition. During the second week of treatment, when the dose is tapered, the patient should report any worsening impairment, so that the tapering can be done more gradually.

Use of long-acting oral corticosteroid preparations (eg, dexamethasone) or shorter-acting drugs given in divided doses is not advisable, since blood levels of exogenous steroids in the early morning hours will suppress the normal endogenous ACTH surge. This is likely to lead to some degree of adrenal atrophy within the 2-week treatment course.[20,21]

Some patients are unable to withdraw from oral corticosteroids due to unequivocal clinical deterioration; these patients appear to be "steroid-dependent." For example, a patient may be ambulatory on steroids but unable to stand when the steroids are tapered. In this situation, it is advisable to attempt very slow tapering of steroids and to attempt to switch to alternate-day use.

For severe exacerbations, intravenous MP may be preferable to oral prednisone.[9,15,16] We administered MP (500 mg/day IV for 3 days) to 75 relapsing MS patients in an outpatient clinic setting, followed by oral prednisone (60 mg/day tapered over 18 days by 10 mg/day every 3 days) without significant complications. Half of the patients showed improvement of ≥1.0 points on the Kurtzke Expanded Disability Status Scale for up to 6 weeks. Insomnia, experienced by 25% of our patients, was effectively treated with sedatives. Cimetidine or ranitidine were administered prophylactically during MP therapy.

Corticosteroid toxicity

Corticosteroid therapy carries certain widely recognized risks, including salt and fluid retention, hypokalemia, CNS side effects, gastrointestinal side effects, and osteoporosis. Fluid retention is usually of minor importance, except in patients with barely compensated heart disease, in whom it can worsen congestive failure. Fluid retention can be minimized by salt restriction during the course of therapy; the use of a diuretic agent is strongly discouraged due to the exaggerated risk of hypokalemia. Ankle edema can be minimized by elastic stockings and leg elevation.

Hypokalemia is usually not a problem in the absence of concurrent potassium wasting, such as with diuretic therapy, but in the presence of heart disease or with concurrent diuretic therapy, oral potassium replacement should be administered and the electrolytes monitored during therapy. Rarely, an MS patient will develop symptomatic hypokalemia during ACTH therapy, usually manifested as progressive generalized weakness during the second week of therapy.

Gastrointestinal side effects are usually minor and of little importance in the absence of peptic ulcer disease. Cimetidine or ranitidine should be administered concurrently in a patient with a history of ulcer. CNS side effects from steroids or ACTH can be substantial problems in MS patients. Patients most commonly experience anxiety and difficulty sleeping. However, they may have more severe reactions consisting of very significant depression, mania, or (rarely) psychosis. Osteoporosis can be minimized by avoiding chronic use of steroids, by maximizing mobility and exercise, and, when necessary, by chronic administration of calcium and vitamin D.

SPASTICITY

One of the cardinal clinical features of MS is the upper motor neuron syndrome, which can occur with lesions of the spinal cord, brain stem, or cerebrum. The term "spasticity" is imprecise and difficult to clearly define. The condition is characterized by weakness, loss of dexterity, and the inability to produce isolated movements. Spasticity is usually accompanied by clinical features that derive from disinhibited anterior horn cells. The latter include increased muscle tone, hyperreflexia, and limb spasms. The mechanisms which produce spasticity are complex and poorly understood but are believed to involve interruption of inhibitory pathways which descend to spinal segmental levels. As a result, the anterior horn cells become hyperexcitable.

Spastic hypertonia may be accompanied by very disagreeable clinical symptoms such as stiffness, spasms, and pain. Patients report uncomfortable stiffness or tightness in affected limbs. Involuntary triple flexion or extension, usually affecting the legs, may occur spontaneously or may be precipitated by attempts at voluntary movement, changes in position, or various cutaneous or painful stimuli. These brief and often painful spasms may be infrequent, intermittent, or nearly continuous. Nocturnal spasms may interfere with sleep, and daytime spasms may interfere with ambulation. In addition, patients may complain of symptomatic clonus, which is usually described as shaking or tremor. Patients may exhibit spastic hypertonia out of proportion to underlying muscle weakness. In such a situation, alleviation of spasticity may improve motor function or unmask the potential for rehabilitation.

'Beneficial' effects

Ironically, certain effects of spasticity may be considered beneficial and actually may be lost with effective treatment. For example, increased muscle tone in lower-extremity extensor muscles due to spasticity may be important in supporting an individual's weight during walking or patient transfer.

A common adverse effect with antispastic drugs is concomitant muscle weakness. The physician needs to be very cautious in treating spasticity in a patient who is barely ambulating due to leg weakness. Hyperactive flexor spasms under some circumstances can be seen as protective, because the limb is withdrawn from potentially harmful stimuli. Flexor spasms may also protect a limb from atrophy due to disuse, or from osteoporosis due to immobility, and may even play a role in reducing deep venous thrombosis.

Despite these cautions, pharmacotherapy for spasticity may effectively alleviate spastic hypertonia, symptomatic clonus, and leg spasms. Pharmacotherapy should be combined with more basic management techniques, including proper bed positioning and avoiding noxious stimuli. Urinary tract infections or pressure sores that go unrecognized may intensify spasticity and should be suspected and treated early and aggressively. Tightly fitting clothes should be loosened, since cutaneous stimuli will increase spastic hypertonia and precipitate spasms. Bowel and bladder function should be monitored and optimized to prevent fecal impaction or bladder distention. A program of regular range-of-motion exercises for the limbs will be helpful in preventing contractures and may reduce the degree of spasticity for several hours.

Baclofen

A number of drug options are available to treat spasticity.[22,23] Practical choices include baclofen and diazepam, which act centrally, and dantrolene, which acts at the level of the muscle.

Baclofen is the drug of choice for symptomatic spasticity in MS.[24] It probably exerts an antispastic effect by interacting with receptors for the inhibitory neurotransmitter, gamma-aminobutyric acid.[23] In this way, baclofen inhibits calcium influx into presynaptic terminals, thereby suppressing release of excitatory neurotransmitters. The initial dosage is 5 to 10 mg tid, with intermittent upward dosage adjustments to achieve a therapeutic response or maximum tolerated dose. The patient can usually be instructed to gradually increase the dosage by making small biweekly adjustments of 10 mg per total 24-hour dose. The patient should be instructed to phone at 4-week intervals to consult about the effect of the drug, possible adverse side effects, and the need for further dosage adjustment. The maximum daily dosage is unknown, although many clinicians are reluctant to exceed 80 mg. Occasionally, the baclofen dose can be increased gradually to 300 to 400 mg/day, with benefits emerging only at a very high dose.

Baclofen has been associated with few serious side effects. The principal limitations are confusion, sedation, or increased muscle weakness. Confusion or sedation occur principally in patients with substantial forebrain involvement and clearly advanced disease. These side effects can be minimized or prevented by initiating the drug at a very low dose with very slow dose increments, according to the particular needs of the patient. A common strategy is to initiate therapy with 5 or 10 mg taken prior to predictable times of increased symptoms (eg, bedtime), with 5-mg increases every 4 to 7 days.

An occasional problem with baclofen is increased weakness, particularly in patients barely ambulating due to lower-extremity weakness. The patient should be cautioned against abrupt baclofen withdrawal, since confusional states or seizures have been reported.[25] An increased incidence of ovarian cysts has been observed in rats treated with baclofen. The magnitude of this risk in women is uncertain but is probably very low.

Diazepam

Some patients find the use of benzodiazepines helpful, and drugs in this category can be particularly useful for patients with bothersome spasticity and anxiety. Their antispastic effect probably relates to enhancement of gamma-aminobutyric acid-mediated presynaptic inhibition at the level of the spinal cord.[23] Diazepam is usually initiated at a dose of 2 mg bid or tid, with gradual increments over a period of weeks to a maximum dosage of 20 mg tid. Patient dependence is one of the principal problems with diazepam. It must be withdrawn gradually, and at times this is a difficult process. Many patients experience troublesome CNS side effects, including dizziness, drowsiness, distractibility, and confusion. Finally, one must exercise caution in prescribing diazepam for patients with serious depression because of the possibility of intentional overdosage.

Particularly difficult spasticity may occasionally respond well to the combination of baclofen and small doses of diazepam (0.5 to 1 mg bid). This may be due to diazepam's potentiation of the central effect of baclofen. Such a low dose is not usually associated with sedation.

Dantrolene

For patients who can't tolerate or don't respond well to baclofen or diazepam, dantrolene may be an effective alternative. Dantrolene exerts an antispastic effect by a peripheral mechanism: it prevents activation of myofibril contraction.[26] However, dantrolene use consistently results in muscle weakness, a side effect that may be of little importance to a nonambulatory patient but which represents a relative contraindication for its use in patients ambulating with difficulty due to leg weakness. The drug appears to have relatively little effect on cardiac or smooth muscle but should be used cautiously in patients with myocardial disease. Dantrolene is initiated at a dosage of 25 mg daily and is gradually increased to a maximum dosage of 100 mg qid. Dosage increments should be made at semiweekly intervals so that the lowest effective dosage can be maintained. Some patients can be given dantrolene in a single bedtime dose, particularly if spasms are problematic only at night.

The principle important side effect of dantrolene is toxic hepatitis.[27] The incidence of this potentially fatal adverse event increases with dosages above 400 mg/day and is more common in women and patients over age 35. Most but not all patients develop anorexia, nausea, and vomiting. Asymptomatic transaminasemia may herald the onset of symptomatic toxic hepatitis; therefore, transaminase levels should be checked prior to initiating dantrolene and should be monitored biweekly in every patient taking the drug. The clinician should also monitor the effect of and need for

dantrolene. If a therapeutic response has not been achieved in a reasonable period of time, the drug should be discontinued because of potential hepatotoxicity. The principal minor side effect of dantrolene is diarrhea; this usually responds to lowering the dosage. Occasionally, pleuritis and pericarditis occur as part of a hypersensitivity reaction.[28]

Selecting antispastic drugs

Some patients respond better to one antispastic drug than to another, but it is not clear how to predict the best drug in individual patients. Baclofen should be the drug of choice when initiating therapy, with small doses of diazepam added if baclofen is inadequately effective. A trial of dantrolene can be considered only when severe and intractable spasticity interferes with function or hygiene.

Recent experience with intrathecal baclofen suggests a potential role for this route of administration in carefully selected patients. Penn and colleagues reported markedly reduced muscle tone and spasms with continuous intrathecal baclofen infusion in 10 patients with MS and in 10 patients with spasticity from spinal cord trauma.[29] Beneficial effects were evident for as long as 3 years. The indications for intrathecal baclofen in MS patients are not yet clear, but this appears to be an attractive therapeutic option for patients with severe disabling spasticity that cannot be managed effectively with oral medications.

PAROXYSMAL DISORDERS

Dystonic spasms

Paroxysmal disorders in MS include dystonic spasms, seizures, tic douloureux, and episodic paresthesias. Dystonic spasms or "tonic seizures" occur in a small proportion of patients[30] and consist of brief, recurrent, painful posturing of one or more extremities. Dystonic spasms more commonly involve one upper extremity but can involve any combination of limbs. They are not associated with epileptiform electroencephalographic abnormalities, altered consciousness, or involuntary micturition but may be associated with relatively inconspicuous distal clonic movements.

Dystonic spasms are mostly spontaneous but may be precipitated by voluntary movement or by cutaneous or painful stimuli. Episodic dystonic spasms appear to respond well in most instances to carbamazepine.[31] Low doses of this drug often provide total control of spasms; it may not be necessary to achieve a blood level as high as 8 to 12 µg/mL, commonly used as the an-

ticonvulsant "therapeutic range." Therapy is initiated at 200 mg bid, which is usually well tolerated, even by ataxic patients. Other anticonvulsants, notably phenytoin, have been used, but in our experience they are less effective than carbamazepine. These spasms do not appear to be particularly responsive to baclofen.

Seizures

Seizures occur in approximately 5% to 10% of MS patients at some point in their illness[32,33] and usually take the form of a single generalized tonic-clonic seizure which generalizes from a focal origin. Patients with MS rarely present with seizures; these are most common in later stages of the disease. Status epilepticus has been reported, usually in late stages of MS associated with active disease (personal communication).

Drug therapy

Generalized motor seizures in MS can usually be readily controlled with phenytoin in doses adequate to achieve a therapeutic blood level. Carbamazepine also can be used, but patients with significant axial instability often find their ataxia increased by carbamazepine, particularly when it is initially administered in high doses to rapidly achieve a therapeutic blood level. As with seizures from any cause, blood should be monitored for drug toxicity and anticonvulsant blood levels to guide therapy and check compliance.

Status epilepticus, though rare, can be a difficult management problem in MS (personal communication). The use of barbiturates or long-acting benzodiazepines, such as lorazepam, although usually effective in controlling the spells, may be associated with prolonged postictal obtundation or confusion, in our experience lasting as long as 2 weeks. We have had better experience with intravenous phenytoin administered at a rate of 50 mg/minute to a dose of 15 mg/kg, followed by phenytoin maintenance.

BLADDER DYSFUNCTION

In MS, symptoms referable to bladder dysfunction occur in at least two thirds of patients[34,35] and are a significant source of distress, as this problem can be socially disabling. Fortunately, bladder symptoms are amenable to effective pharmacotherapy.

The management of bladder symptoms in MS starts with an assessment of the underlying pathophysiology. Possible evaluation procedures range from simple bed-

side testing to complex cystometrograms with sphincter electromyography.[36,37] Every MS patient reporting bladder symptoms should have a urinalysis and a urine culture to determine the presence or absence of a urinary tract infection and a postvoid residual urine volume assessment to detect urinary retention. Patients with recurrent urinary tract infections or incontinence that does not respond to the simple measures described below should be referred to a urologist.

Irritable bladder

Most commonly, patients report urgency, frequency, and urge incontinence, symptoms suggesting a small-capacity, irritable bladder resulting from spontaneous detrusor muscle spasm. Anticholinergic drugs are the initial pharmacotherapy for irritative bladder symptoms in the absence of infection. Oral propantheline bromide may be initiated at a dosage of 15 mg qid and gradually increased until symptoms are relieved or distressing side effects occur (eg, dry mouth, blurred vision, or worsening constipation). In patients particularly sensitive to anticholinergic side effects, propantheline bromide can be started at 7.5 mg bid and gradually increased. Oral oxybutynin, 5 mg as often as four times a day, is an alternative anticholinergic. Propantheline bromide or oxybutynin can be used intermittently, particularly if the irritative symptoms are distressing at a particular time, such as at night or before a long automobile ride.

One of the common significant adverse effects of anticholinergic drugs in this setting is urinary retention. Consequently, the postvoid urinary residual volume should be checked after initiating therapy. The patient should be informed about the possibility of urinary retention when starting anticholinergics. If significant retention occurs, a bladder self-catheterization program can be added to anticholinergic drug therapy. Patients failing to achieve urinary continence with anticholinergic pharmacotherapy, with or without self-catheterization, need formal urologic evaluation.

Urinary tract infection

Bacterial urinary tract infection is common in MS, and increased neurologic dysfunction due to fever commonly accompanies the infection. Sepsis from inadequately treated or untreated urinary tract infection is unfortunately a common cause of severe illness or even death in late stages of this illness.

The principles of antimicrobial therapy are not significantly different in MS than in other conditions. It is important, however, to rigidly adhere to certain practices. Every MS patient with a significant change in urinary tract symptoms, or with a fever without urinary tract symptoms, must have urine examined both microscopically and by culture and sensitivity test. A urinalysis is also usually indicated during times of a flare in MS symptoms, even with minimal fever or change in bladder symptoms.

If an infection is likely, it is important to hydrate the patient and treat the fever symptomatically, and it is reasonable to begin antimicrobial therapy pending the results of the culture and sensitivity tests. It is always necessary to check the results of the culture and adjust antibiotic therapy accordingly. "Blind" therapy with broad-spectrum antibiotics such as sulfisoxazole, ampicillin, or sulfamethoxazole and trimethoprim is discouraged, since unusual or resistant organisms are common—particularly in patients in advanced stages of the disease, with recurrent infection, or with an indwelling catheter. Recurrent urinary tract infection in the MS patient is an indication for urologic consultation.

When a patient has suffered recurrent urinary tract infection, prophylaxis with low dosages of broad-spectrum antibiotics such as sulfamethoxazole and trimethoprim, nitrofurantoin, or methenamine mandelate is empirically indicated. Methenamine mandelate is a nonspecific agent which is hydrolyzed to formaldehyde, the active antimicrobial agent, and ammonia. The hydrolysis occurs only in acid urine, so urinary pH should be checked and ascorbic acid added if necessary. Diagnostic evaluation of the urinary tract is necessary in cases of recurrent infections. This evaluation should include an intravenous pyelogram to rule out upper urinary tract pathology and lower urinary tract structural disease such as bladder diverticula; a urologic evaluation is also usually advisable in this situation.

CEREBELLAR ATAXIA

Cerebellar ataxia is one of the most disabling of all the clinical manifestations of MS, and also one of the least responsive to pharmacotherapy. Isoniazid has been reported to effectively reduce cerebellar tremor in some MS patients,[38] but the therapeutic effect required doses as high as 1,200 mg/day. In our experience, the effect of high doses of isoniazid on disabling cerebellar tremor has been disappointing. In view of the risk of hepatotoxicity associated with high-dose isoniazid therapy and the limited prospects for functional im-

provement, injudicious use of isoniazid is unwise. When initiating a trial of isoniazid or other agents for cerebellar tremor, precautions should be taken to monitor for hepatotoxicity, and the response to the agent should be assessed carefully in terms of functional improvement or deterioration. After several weeks, if no significant benefit is seen, the trial should be discontinued.

Various other pharmacotherapies for cerebellar tremor have been tried with limited success, including baclofen, carbamazepine, clonazepam, propranolol, choline, lecithin, meprobamate, and mysoline. At this time, clonazepam appears to be the drug of choice for disabling cerebellar tremor. The dose can be initiated at 0.5 mg at bedtime and increased gradually to an end point of sedation or effective control of cerebellar tremor. It is rarely advisable to increase clonazepam to a dose greater than 2 mg qid.

NEUROBEHAVIORAL MANIFESTATIONS

Neurobehavioral syndromes are common and varied in MS.[39] They include depression and hard-to-classify emotional distress, cognitive impairment, emotional lability, anxiety, and, more rarely, bipolar disease or psychosis. Physicians need to understand and be able to recognize these syndromes in order to provide information and support to patients, families, and employers, and to make appropriate referrals. Drug therapy plays an important adjunctive role here, since all of the syndromes except cognitive dysfunction are directly amenable to pharmacotherapy.

Depression

Depression is common in MS and far exceeds the frequency seen in control groups.[40] Its etiology and mechanisms are unknown, but it appears to be more common in MS patients with cerebral involvement than in those with disease affecting predominantly the spinal cord, suggesting an organic etiology.[41] Other investigators have suggested that emotional distress and depression results from recurrent losses combined with the unpredictable nature of symptoms and disease course. Depression may occur recurrently or as part of bipolar disease and is the source of significant morbidity and mortality, since suicide or attempted suicide is a clear risk. Assessing the presence and severity of depression in MS is important, even if the patient does not appear depressed.

Many patients with mild and transient depression can be managed with supportive measures alone.

These include establishing a mechanism for the patient and family to contact the treating physician and removing potentially dangerous sedative, anxiolytic, or analgesic drugs from the patient's environment because of the risk of intentional overdosage. More severe depression is best managed by adding a tricyclic antidepressant to the supportive measures. We have most frequently used amitriptyline 150 mg/day (either at bedtime or 50 mg tid) or nortriptyline 100 to 150 mg at bedtime. Treatment should be instituted gradually to minimize anticholinergic or CNS side effects. Amitriptyline is initiated at 50 mg at bedtime and increased over several weeks to 150 mg/day. The patient and family should be warned of the delay between initiating therapy and observing a benefit. The patient should be monitored carefully for worsening of the depression during the initial month of therapy.

Some patients with severe forebrain involvement experience confusion due to the anticholinergic effects of amitriptyline. For these patients, nortriptyline or desipramine are often acceptable tricyclic anticholinergic drugs. Patients with the combination of depression and bladder impairment may benefit from the tricyclic antidepressant, imipramine, which has antidepressant, anticholinergic, and alpha-adrenergic effects. The last two effects may be useful in treating symptoms of an uninhibited spastic bladder. Patients who are unable to tolerate the anticholinergic side effects of tricyclics, or who experience weight gain as an adverse effect, may use fluoxetine 20 to 40 mg qd as an alternative.

Emotional lability

The syndrome of pathological laughing and weeping is common in MS. Its severity ranges from a barely noticeable tendency to giggle or tear readily to a less common but very distressing syndrome of powerful paroxysmal emotional outbursts. Emotional lability is most commonly part of a larger syndrome of pseudobulbar palsy, accompanying other evidence for bilateral corticobulbar and corticospinal disease.

The clinician needs to be able to recognize the syndrome of emotional lability. Its potential impact on the patient cannot be overstated: many patients consider the inability to control emotional display to be more distressing than bladder or even bowel incontinence. Its effect on interpersonal relationships can be devastating. Also, pathological laughing can mask a severe underlying depression, which itself may be partly a reaction to "emotional incontinence."

In many instances this syndrome is directly treatable. Amitriptyline in low doses is often remarkably effective.[42] Typically, therapy is initiated at 25 mg bid, increasing to 25 mg tid in the absence of a therapeutic response. The drug can be periodically tapered to assess the need to continue therapy. Other tricyclic antidepressants may have a similar effect, as may dopaminergic drugs such as levodopa or bromocriptine.

Anxiety and psychosis

For reasons that are unclear, MS is associated with anxiety that approaches panic in some patients. Factors such as the uncertainty of future symptoms or impairment may contribute to this anxiety. Alprazolam, a benzodiazepine analogue, has been useful in treating some of these patients. A dosage of 0.25 to 0.50 mg bid or tid is usually sufficient. Diazepam can be used as an alternative. As with other symptomatic therapies, the need for pharmacotherapy over time should be intermittently assessed and the drug tapered off if appropriate, since these drugs may worsen underlying depression or cognitive dysfunction.

Psychosis is occasionally seen in MS and may even be a presenting manifestation. Because of its rarity, however, the actual relationship between the thought disorder and MS is conjectural. The use of antipsychotic drugs may occasionally be required; their use in MS patients is not different than in the psychiatric population.

FATIGUE

Fatigue, a significant problem for many MS patients, is an umbrella term used to describe a variety of problems. A feeling of overwhelming exhaustion commonly accompanies MS and can be disabling. It tends to come on late in the day, often interfering with activities. Amantadine, 100 mg bid, may be effective in treating this syndrome[43]; pemoline, 37.5 mg in the morning, has been used by some clinicians.[44]

PAIN

The frequency with which MS patients experience significant pain is underestimated by physicians. The reported prevalence varies from 28.8% to 82%. In reviewing 159 MS patients followed in a hospital MS clinic, Moulin et al[45] divided pain into acute and chronic syndromes. Acute pain was typically stereotyped, short in duration, and paroxysmal,

whereas chronic pain was often more continuous and present for a period of at least 1 month with no other obvious cause. Chronic headache and pain controlled by aspirin or acetaminophen were excluded from that study. Women were more often affected by pain, and increasing age and longer disease durations were also predictors of this problem.

Acute pain

In Moulin's study, 9% percent of the subjects suffered attacks of pain. Pain syndromes were heterogeneous. Various types of facial pain can occur, including classical trigeminal neuralgia[46] or more atypical facial pain.[47] Both are likely caused by disease in the pontine tegmentum. Trigeminal neuralgia is characterized by brief attacks of intense stabbing or electric shock-like sensations in the distribution of the second and third divisions of the trigeminal nerve. The clinical presentation is identical to idiopathic trigeminal neuralgia, except patients are younger and the pain is more often bilateral.

Episodic facial pain is a difficult therapeutic problem. In general, it does not respond well to analgesics, although aspirin, acetaminophen, or newer nonsteroidal anti-inflammatory agents may alleviate the pain to a slight degree. Carbamazepine is the drug of choice for the treatment of episodic facial pain. We have at times found it necessary to gradually increase the dose to achieve blood levels of 6 to 8 μg/mL to elicit a response. Some patients respond better to the combination of perphenazine and amitriptyline.[48] Therapy is usually begun with the combination of 2 mg perphenazine and 25 mg amitriptyline bid, with gradual weekly upward dose adjustments to a maximum of 12 mg perphenazine and 150 mg amitriptyline. The neuroleptic perphenazine is a piperazine derivative of phenothiazine. Possible complications of that category of drug include drug-induced parkinsonism, tardive dyskinesia, hepatitis, and the neuroleptic-malignant syndrome. Amitriptyline, phenytoin, or baclofen monotherapy are alternative approaches for patients who cannot be managed effectively with carbamazepine or the combination of perphenazine and amitriptyline. If medical treatment fails, percutaneous trigeminal rhizotomy may provide pain relief.

Paroxysmal limb pain may also occur. This commonly takes the form of painful episodic paresthesias, which occur in less than 5% of patients.[49] It presents as a brief tic-like pain, less often burning dysesthesia lasting up to 1 minute. The pain may occur spontaneously or may follow a limb movement, tactile stimulation of

the affected limb, or hyperventilation. Treatment is similar to medical therapy outlined for trigeminal neuralgia. Painful tonic spasms, discussed above, were uncommon in Moulin's study (1.25%)[45] but were more frequent in a Japanese study (17%).[49] Lhermitte's phenomenon is common in MS patients (33% to 38%) but only rarely produces significant pain.

Chronic pain

Chronic pain syndromes are common, though less well recognized by practitioners. In Moulin's series,[45] 48% of the patients suffered from one or more chronic pain syndromes. Dysesthetic limb pain is by far the most common of these, accounting for 29% of the MS patients in Moulin's study. This is most commonly described as burning or tingling pain and is often associated with myelopathy, Lhermitte's phenomenon, or with transverse myelitis. The pain may be primarily nocturnal and may worsen with temperature elevations or abrupt changes in the weather. Posterior column dysfunction with loss of vibratory or position sense in the feet is commonly present when spinothalamic pathways mediating pain sensation are intact. Tricyclic antidepressants are the first choice in treatment of chronic pain, but the response rate is only between 20% and 40%. Anticonvulsant drugs have also been tried but are not particularly effective. A transcutaneous electrical nerve stimulator, or TENS, unit and cognitive behavioral therapy may be useful for patients who fail other measures. Narcotic analgesics should be avoided.

Chronic back pain is extremely common and may occur for a number of reasons. Pain may occur primarily because of mechanical stresses caused by ataxia and weakness. This type of pain is usually confined to the back but may involve the buttocks, hips, and legs, depending on the pathogenesis. The pain rarely radiates below the knees. Patients who experience this problem frequently have significant osteoarthritic change on radiography or postural difficulties associated with weakness and spasticity created by MS. Therapy initially involves nonsteroidal anti-inflammatory drugs and physical therapy to improve posture and restore strength and tone to abdominal and paraspinal muscles. Occasionally a walking aid, ankle-foot orthosis for foot drop, or proper seating in a wheelchair may be helpful. Myofascial pain and trigger points often respond to stretch and spray techniques but may require injection of a local anesthetic. Leg pain, especially if radicular in nature, extending below the knee to the ankle, should be investigated to exclude a coexistent herniated disc.

CONCLUSION

Pharmacologically altering the natural history of the underlying disease process at work in MS is still mostly experimental. However, clinical experience shows that symptoms associated with MS can be effectively controlled using proven pharmacologic agents. Symptomatic drug therapy, carefully selected and closely monitored to avoid or minimize side effects, is a key part of the multidisciplinary management of patients with MS.

REFERENCES

1. Goodkin DE, Ransohoff RM, Rudick RA. Clinical trials of experimental therapies in MS: current status. Part 1. Cleve Clin J Med 1992; 59: 63–74.
2. Troiano R, Hafstein M, Ruderman M, et al. Effect of high-dose intravenous steroid administration on contrast-enhancing computed tomographic scan lesion in multiple sclerosis. Ann Neurol 1984; 15:257–263.
3. Troiano R, Hafstein M, Zito G, et al. The effect of oral corticosteroid dosage on CT-enhancing multiple sclerosis plaques. J Neurol Sci 1985; 70:67–72.
4. Compston DAS, Milligan NM, Hughes PJ, et al. A double-blind controlled trial of high dose methylprednisolone in patients with multiple sclerosis: 2. laboratory results. J Neurol Neurosurg Psychiatry 1987; 50:517–522.
5. Smith T, Seeberg I, Sjo O. Evoked potentials in multiple sclerosis before and after high dose methylprednisolone infusion. Eur Neurol 1986; 25:67.
6. Troiano R, Cook SD, Dowling PC. Steroid therapy in multiple sclerosis: point of view. Arch Neurol 1987; 44:803–807.
7. Maida E, Summer K. Serum cortisol levels in multiple sclerosis patients during ACTH treatment. J Neurol 1979; 220:143–148.
8. Snyder BD, Lakatua DJ, Poe RP. ACTH-induced cortisol production in multiple sclerosis. Ann Neurol 1981; 10:388–389.
9. Durelli L, Cocito D, Riccio A, et al. High-dose intravenous methylprednisolone in the treatment of multiple sclerosis: clinical-immunologic correlations. Neurology 1986; 36:238–243.
10. Naess A, Nyland J. Effect of ACTH treatment on CSF and blood lymphocyte subpopulations in patients with multiple sclerosis. Acta Neurol Scand 1981; 63:57–66.
11. Kirk P, Compston A. The effect of methylprednisolone on lymphocyte phenotype and function in patients with multiple sclerosis. J Neuroimmunol 1990; 26:1–8.
12. Kastrokoff LF, Paty DW. A serial study of peripheral blood T lymphocyte subsets in relapsing-remitting multiple sclerosis. Ann Neurol 1984; 15:250–256.
13. Rose AS, Kuzma JW, Kurtzke JF, Namerow NS, Sibley WA, Tourtellotte WE. Co-operative study in the evaluation of therapy in multiple sclerosis: ACTH versus placebo. Neurology 1970; 20(part 2):1–59.
14. Dowling PC, Bosch UV, Cook SK. Possible beneficial effect of high dose intravenous steroid therapy in acute demyelinating disease and transverse myelitis. Neurology 1980; 30:33–36.

15. Barnes MP, Bateman DE, Cleland PG, et al. Intravenous (IV) methylprednisolone for multiple sclerosis in relapse. J Neurol Neurosurg Psychiatry 1985; 48:157–159.

16. Milligan NM, Newcombe R, Compston DAS. A double-blind controlled trial of high dose methylprednisolone in patients with multiple sclerosis: 1 clinical effects. J Neurol Neurosurg Psychiatry 1987; 50:511–516.

17. Fog T. The long-term treatment of multiple sclerosis with corticoids. Acta Neurol Scand 1965; 41(2)(Suppl 13):473–484.

18. Miller H, Newell DJ, Ridley A. Multiple sclerosis. Treatment of acute exacerbations with corticotrophins (ACTH). Lancet 1961; 2:1120–1122.

19. Millar JHD, Vas CJ, Norona MJ, et al. Long term treatment of multiple sclerosis with corticotrophin. Lancet 1967; 2:429–431.

20. Salassa RM, Bennett WA, Keating FR, Sprague RG. Postoperative adrenal cortical insufficiency: occurrence in patients previously treated with cortisone. JAMA 1953; 152:1509.

21. Byyny RL. Withdrawal from glucocorticoid therapy. New Eng J Med 1976; 295:30–32.

22. Young RR, Delwaide PJ. Spasticity. N Eng J Med 1981; 304:28–33,96–99.

23. Davidoff RA. Antispasticity drugs: mechanisms of action. Ann Neurol 1985; 17:107–116.

24. Feldman RG, Kelly-Hayes M, Conomy JP, Foley JM. Baclofen for spasticity in multiple sclerosis. Double-blind crossover and three-year study. Neurology 1978; 28:1094–1098.

25. Terrence CF, Fromm GH. Complications of baclofen withdrawal. Arch Neurol 1981; 38:588–589.

26. Hainaut K, Desmedt JE. Effect of dantrolene sodium on calcium movements in single muscle fibres. Nature 1975; 252:728–729.

27. Utili R, Boitnott JK, Zimmerman HJ. Dantrolene-associated hepatic injury: incidence and character. Gastroenterology 1977; 72:610–616.

28. Petusevsky ML, Faling LJ, Rocklin RE, et al. Pleuropericardial reaction to treatment with dantrolene. JAMA 1979; 242:2772–2774.

29. Penn RD, Savoy SM, Corcos D, et al. Intrathecal baclofen for severe spinal spasticity. N Eng J Med 1989; 320:1517–1521.

30. Joynt RJ, Green D. Tonic seizures as a manifestation of multiple sclerosis. Arch Neurol 1962; 6:293–299.

31. Berger JR, Sheremata WA, Melamed E. Paroxysmal dystonia as the initial manifestation of multiple sclerosis. Arch Neurol 1984; 41:747–750.

32. Trouillas P, Courjon J. Epilepsy with multiple sclerosis. Epilepsia 1972; 13:325–333.

33. Cendrowski W, Majkowski J. Epilepsy in multiple sclerosis. J Neurol Sci 1972; 17:389–398.

34. Kaplan SA, Blaivas JG. Managing the multiple sclerosis patient who has bladder dysfunction. Contemp Urol 1989; 1:24–33.

35. Smith CR, Scheinberg LC. Clinical features of multiple sclerosis. Semin Neurol 1985; 5:85–93.

36. Blaivas JG. Management of bladder dysfunction in multiple sclerosis. Neurology 1980; 30(2):12–18.

37. Wein AJ. Classification of neurogenic voiding dysfunction. J Urol 1981; 125:605–609.

38. Hallett M, Lindsey JW, Adelstein BD, Riley PO. Controlled trial of isoniazid therapy for severe postural cerebellar tremor in multiple sclerosis. Neurology 1985; 35:1374–1377.

39. Schiffer RB, Slater RJ. Neuropsychiatric features of multiple sclerosis. Recognition and management. Semin Neurol 1985; 5:127–133.

40. Schiffer RB, Babigian HM. Behavioral disorders in multiple sclerosis, temporal lobe epilepsy, and amyotrophic lateral sclerosis. An epidemiologic study. Arch Neurol 1984; 41:1067–1069.

41. Schiffer RB, Caine ED, Bamford KA, Levy S. Depressive episodes in patients with multiple sclerosis. Am J Psych 1983; 140:1498–1500.

42. Schiffer RB, Herndon RM, Rudick RA. Treatment of pathologic laughing and weeping with amitripyline. N Eng J Med 1985; 312:1480–1482.

43. Murray TJ. The treatment of fatigue in MS [Abstract]. Neurology 1984; 34(Suppl 1):139

44. Bass B, Weinshenker BG, Penman M, Ebers GC, Rice GPA. A double-blind, placebo-controlled, randomized trial to compare the efficacy of cylert (pemoline and placebo in the control of fatigue in multiple sclerosis) Neurology 1992; (in press).

45. Moulin DE, Foley KM, Ebers GC. Pain syndromes in multiple sclerosis. Neurology 1988; 38:1830–1834.

46. Jensen TS, Rasmussen P, Reske-Nelsen E. Association of trigeminal neuralgia with multiple sclerosis: clinical and pathological features. Acta Neurol Scand 1982; 65:182–189.

47. Clifford DB, Trotter JL. Pain in multiple sclerosis. Arch Neurol 1984; 41:1270–1272.

48. Monks R, Merskey H. Psychotropic drugs. [In] Wall PD, Melzack R, eds. Textbook of pain. Edinburgh: Churchill Livingstone, 1984:530.

49. Shibasaki H, Yoshigora K. Painful tonic seizure in multiple sclerosis. Arch Neurol 1974; 30:47–51.