• Major Depressive Disorder – Treatment Options Other Than SSRI
  *Dr Lam Tat Chung, Paul (林達聰醫生)*

• Long-term Treatment of Relapsing-Remitting Multiple Sclerosis
  *Dr Chan Koon Ho (陳灌豪醫生)*

• The Patient With Daily Headache
  *Dr Hui Che Fai, Andrew (許志輝醫生)*
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Editorial

In primary care settings, approximately 30% to 50% of patients have prominent psychiatric symptoms or identifiable mental disorders, which are of significant adverse consequences if left untreated. Even in surgical specialties, many presurgical and postsurgical developments are associated with significant mental health issues. Recent trends in medicine promote the further integration of psychiatry into the mainstream of medical practice, and emphasize the importance of attending to patients with psychiatric symptoms regardless of the clinician’s medical specialty. We hope this issue of the Journal will remind our readers of this important aspect of patient care.

References:
Depression is a complex syndrome that includes many different symptoms. With depressive mood as a core symptom, the condition is also associated with tiredness, loss of drive and motivation, poor concentration and cognitive functioning, impairment of attention or alertness, anhedonia and sexual dysfunction, agitation and irritability, aggression, anxiety, hypersomnia or insomnia, feeling of guilt, suicidality, dyscontrol of appetite and weight, and many associated physical symptoms.

The pharmacological treatment of depression evolves around the understanding and manipulation of the monoamine systems, namely the serotonergic, noradrenergic and dopaminergic systems. The interplay between these systems is not fully understood, but the adequacy and proper functioning of each of the monoamines has been shown to be important for the maintenance of a normal mood. Drugs have been developed to target each of the three systems to alleviate the disorder.

Currently, the most widely prescribed group of drugs for the treatment of depression is the selective serotonin reuptake inhibitors (SSRIs). This group of drugs is deemed as a great advance over the older antidepressants such as monoamine oxidase inhibitors (MAOIs) and tricyclics in terms of side effect profile and safety. Though a welcomed addition to the armamentarium, there remains many problems and inadequacies that need to be addressed or improved. These include the lack of efficacy in some patients, sexual dysfunction, weight gain, sedation, withdrawal symptoms, etc.

In the Sequenced Treatment Alternative to Relieve Depression (STAR*D) trial, an important large-scale study commissioned by the US National Institute of Mental Health, treatment with the SSRI citalopram for about 10 weeks resulted in a remission rate of only around 30%.

An amotivational syndrome has been described in patients following use of SSRIs for several months. In these patients, although the depression improved, a state of apathy and indifference developed, which could be temporarily alleviated by a dose reduction of the SSRI. The addition of a noradrenergic agent improved the condition. Other problems included bleeding tendencies and the syndrome of inappropriate antidiuretic hormone secretion.

Alternative medications have been developed to address the shortcomings of the SSRIs, and for the group of patients who require treatment for certain specific symptoms in the depressive syndrome by tackling different monoaminergic systems. (Table) While some medications modulate the noradrenergic system, bupropion is the only medication currently available that can effectively target the dopaminergic system as well. Different symptom groups that are controlled by

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**Table. Neurotransmitter effects of antidepressants**

<table>
<thead>
<tr>
<th>Mirtazapine</th>
<th>Norepinephrine/noradrenaline (NE)</th>
<th>Serotonin (5-HT)</th>
<th>Dopamine (DA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>√</td>
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<tr>
<td>Bupropion SR</td>
<td>√</td>
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</tr>
<tr>
<td>Mirtazapine</td>
<td>√</td>
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<tr>
<td>Nefazodone</td>
<td>√</td>
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<tr>
<td>Venlafaxine</td>
<td>√</td>
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</tbody>
</table>

SR = sustained release; SSRI = selective serotonin reuptake inhibitor

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Key words: SSRI (選擇性血清素再吸收抑制劑), major depressive disorder (重度抑鬱症), NDRI (去甲腎上腺素-多巴胺再吸收抑制劑)
the three different monoamines are illustrated in Figure 1.4

Bupropion is a monocyclic ammoketone that has been used for the treatment of major depression since 1989. It belongs to the class of norepinephrine-dopamine reuptake inhibitors (NDRIs). Sustained-release (SR) tablets (150 mg) were available in the US since 1996, and extended-release (XR) tablets (300 mg) since 2003.

Efficacy Studies

A pooled analysis of six randomized controlled trials showed that remission rate with bupropion was similar to SSRIs and better than placebo.5 (Figure 2) Other studies have shown comparable remission rates with escitalopram and venlafaxine.6-9 (Figure 3) Bupropion has also been shown to confer superior benefit in patients complaining of reduced energy, pleasure and interest.10

Treatment Switching

In the STAR*D trial, switching to bupropion SR, sertraline or venlafaxine resulted in similar remission rates of 26% to 28% in patients previously non-responsive to citalopram.11

Combination Therapy

In the above trial, the addition of bupropion SR resulted in a remission rate of 39% in patients previously not responding to citalopram alone. This is much better than the remission rate of 32.9% with buspirone augmentation. Other more favourable outcomes with the bupropion combination include treatment adherence, adverse reaction and change in the Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR) score.12

“Remission rate with bupropion was similar to SSRIs”

Other Benefits

Sexual dysfunction occurs in 20% to 60% of patients treated with SSRIs. This may pose significant distress to depressed patients and compromise their quality of life. Bupropion is not associated with sexual dysfunction including orgasmic dysfunction, sexual arousal disorder and sexual desire disorder.13

Most antidepressants including SSRIs, mirtazapine, tricyclics and MAOIs cause weight gain. No such adverse effect is observed with bupropion. The agent may induce more weight loss than placebo in obese adults.14

Anxiety frequently occurs in depressed patients. Bupropion SR compares favourably with SSRI in the control of anxiety symptoms.15
Adverse Effects

The more frequent adverse effects are headache, insomnia, nausea, vomiting, dry mouth, and sweating.

Special Patient Groups

Bupropion has to be used with care in patients with hepatic failure or renal impairment. Caution should be exercised in patients prone to or with a history of seizures. The agent is classified under FDA Pregnancy Category B, while SSRIs are classified less favourably under Category C.

Conclusion

Bupropion SR (150 mg) given as a single morning dose is an appropriate and efficacious choice for the treatment of patients with major depressive disorder, or for combination therapy with SSRIs. Its unique mechanism of noradrenergic and dopaminergic reuptake inhibition makes it an effective antidepressant, with special benefit for symptoms such as loss of energy and motivation, tiredness, hypersomnia and anhedonia. It has special favourable profiles with regard to sexual function, body weight, control of anxiety symptoms and lack of sedation. In some patients, the dose can be increased to 150 mg twice daily if required.

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  - Comparable antidepressant efficacy with SSRIs
  - Significantly improves fatigue, interest and sleepiness
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  - No weight gain during long term use

- Over 40 million patients treated with Bupropion

- **Wellbutrin SR dosage**

References:

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Long-term Treatment of Relapsing-Remitting Multiple Sclerosis

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Key words: Relapsing-remitting multiple sclerosis (復發緩解型多發性硬化), beta-interferons (乙型干擾素), natalizumab

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disorder characterized by inflammatory demyelination of the central nervous system (CNS). Approximately 85% of patients with classical MS (CMS) have relapsing-remitting MS (RRMS) at onset, characterized by recurrent attacks of inflammatory demyelination and axonal injury affecting different sites of the CNS. About 90% of CMS patients have oligoclonal bands (OCB) in cerebrospinal fluid (CSF). Asians have a lower prevalence of CMS than Caucasians; it has been reported that relatively higher proportions of Asian MS patients have opticospinal MS (OSMS), in which there is predominant involvement of optic nerves and spinal cord, and a lower frequency of CSF OCB. Recent evidence strongly suggests that OSMS is in fact neuromyelitis optica (NMO), also called Devic’s disease, which is distinct from CMS. RRMS patients develop recurrent attacks of inflammatory demyelination affecting the cerebral hemispheres, brainstem, cerebellum, spinal cord (myelitis) and optic nerves (optic neuritis), which are associated with good neurological recovery especially in early attacks; in contrast, relapsing NMO patients typically develop recurrent severe attacks of myelitis and optic neuritis associated with early irreversible neurological disabilities. Importantly, CMS patients are seronegative for NMO-immunoglobulin G (IgG), an autoantibody targeting the aquaporin-4 water channel and a specific biomarker for NMO, while about 60% to 73% of NMO patients are seropositive for NMO-IgG. Hence, early serological testing for NMO-IgG is useful in prompt diagnosis of NMO and its distinction from CMS in patients who present with myelitis or optic neuritis.

Most RRMS patients have satisfactory recovery from acute attacks in the early phase; unfortunately, an accumulating number of patients will develop secondary progressive MS (SPMS) characterized by irreversible progressive neurological deterioration and disability accumulation with or without acute relapses. Natural history studies estimate that RRMS patients develop SPMS at a rate of 2% to 3% per year and the median time to reach the Expanded Disability Status Scale (EDSS) score of 6 (ie, need of unilateral assistance to walk for 100 metres) is estimated to be about 19 years. Axonal degeneration is believed to be the key pathology underlying SPMS. Importantly, axonal injury can occur and be severe early in RRMS. Hence, in the absence of effective treatments that can prevent or delay progression to SPMS, the majority of RRMS patients are at risk of significant neurological disability in the long term in view of the chronic nature and predominantly young onset age of this disorder.

Aetiiological Factors

The exact pathogenetic mechanisms of MS are uncertain. Genetic factors contribute to its aetiology as evidenced by the concordance rate of 31% among monozygotic twins vs 5% for dizygotic twins; moreover, the presence of the HLA-DR2 antigen increases an individual’s susceptibility to CMS. Multiple genes influence the susceptibility to developing MS, but no single gene with the possible exception of HLA has a strong influence. Environmental factors also play a role, as evidenced by the change in MS frequency among individuals and their offspring who migrate into and out of high-prevalence areas. Infection by micro-organisms including herpes simplex virus type 6 and Chlamydia pneumoniae is suggested to be a causative factor, but confirmation from other studies is lacking.

Diagnosis

The diagnosis of RRMS is suggested by a history of recurrent attacks of injury to different sites of the CNS, followed...
by partial or complete resolution of symptoms. Physical findings of abnormalities at multiple CNS sites such as cerebellar ataxia from cerebellar involvement and paraparesis with a sensory level from spinal cord involvement support the diagnosis. Magnetic resonance imaging (MRI) of multiple white matter lesions at different sites of the CNS (ie, spatial dissemination) and lesions with different ages (ie, temporal dissemination, shown by new lesions on repeated MRI) greatly facilitate the diagnosis, especially in patients who presented with the first clinical attack, known as clinically isolated syndrome (CIS), based on fulfillment of the revised McDonald criteria. Lumbar puncture for exclusion of CNS infection and detection of CSF OCB helps to support the diagnosis. Other disorders that mimic RRMS must be excluded, especially relapsing NMO (by testing for NMO-IgG) and vasculitis such as cerebral lupus (by testing for autoantibodies including antinuclear antibody [ANA] and lupus (by testing for autoimmune markers NMO-IgG) and vasculitis such as cerebral lupus (by testing for autoantibodies including antinuclear antibody [ANA] and anti-extractable nuclear antigen [anti-ENA] antibody).

Treatments

Aims and Approach

Treatment aims at: 1) reduction of relapse rate, 2) prevention of fixed disability directly attributable to relapse, 3) symptomatic treatment of fixed neurological deficits, and 4) prevention or delay of development of SPMS, hence minimizing permanent disability. It is encouraged to adopt a multidisciplinary team approach, in which different professionals including neurologist, nurse specialist, physiotherapist, occupational therapist, rehabilitation specialist and clinical psychologist contribute to patient care by providing expertise in management of a chronic neurological disorder. This review will address the long-term pharmacological treatment of RRMS.

Long-term Disease-modifying Drugs

Intravenous pulse methylprednisolone 0.25–1 g daily for 3 to 5 days is indicated during acute attacks associated with potentially significant disability to hasten neurological recovery; however, the benefit on long-term neurological disability is uncertain. Regular intermittent intravenous pulse corticosteroid and regular oral corticosteroid therapies are ineffective for reduction of relapse frequency. Currently, four disease-modifying drugs (DMDs) are approved for use in RRMS. These are beta-interferon (β-IFN) (1a and 1b), glatiramer acetate (GA), natalizumab and mitoxantrone.

Beta-interferon

β-IFN 1a and 1b are first-line immunomodulatory therapies for RRMS. Their short-term efficacy (for 2 to 3 years) in reducing relapse frequency by about one-third is well proven. β-IFN 1a and 1b possess anti-inflammatory properties, inhibit T cell activation and reduce blood-brain barrier permeability to inflammatory cells. Therapy requires subcutaneous injection 3 times a week or on alternate days. Common side effects are local injection site reactions, flu-like symptoms with fever (which tend to subside after several weeks in most patients who continue with therapy), and reversible liver function derangement as evidenced by raised parenchymal liver enzyme levels. In addition, 5% to 30% of treated patients develop persistent neutralizing antibodies that are associated with reduced treatment effect on relapse frequency. Long-term benefits in prevention or reduction of disability are uncertain, and patients or carers need to perform subcutaneous injection. The ideal timing for starting β-IFN in RRMS is controversial. The author is in favour of early initiation of DMD once the diagnosis of RRMS is confirmed and when the disease is active, as evidenced by clinical relapse or MRI evidence of subclinical active inflammation.

Glatiramer Acetate

GA is a synthetic co-polymer structurally similar to myelin basic protein (MBP). Therapy requires daily subcutaneous injection. GA is thought to induce T cell anergy, inhibition of MBP-reactive T lymphocytes and induction of T helper 2 lymphocytes, resulting in an anti-inflammatory action. GA reduces relapse frequency of RRMS by about 30%, and improves MRI parameters of disease activity. Its efficacy is similar to that of β-IFN. GA is generally safe and well tolerated. Similar to β-IFN, its benefit on long-term disability is uncertain.

Natalizumab

Lymphocyte migration across the blood-brain barrier is an important early step in the formation of lesions in MS. α4 integrins are a family of adhesion molecules expressed on the surface of lymphocytes, functioning as an important mediator of cell adhesion and transendothelial migration, and a regulator of immune cells activation within inflamed tissue. Natalizumab is a humanized monoclonal antibody against the α4 integrins, which selectively blocks the binding of α4β1 and α4β7 integrins to their endothelial receptors, hence inhibiting migration of lymphocytes into the brain and reducing inflammation.

A randomized double-blind trial of 213 patients with RRMS or relapsing SPMS treated with intravenous natalizumab (3 mg/kg or 6 mg/kg) or placebo every 28 days for 6 months showed that active treatment was associated with reductions in relapse frequency and the number of new enhancing brain lesions over the 6-month period. However, such differences disappeared upon an additional 6 months’ follow-up. More recently, natalizumab was shown to be effective in RRMS by reducing the relapse rate at 1 year by 68%, and the risk of sustained progression of disability by 42% over 2 years in a 2-year phase III clinical trial. The cumulative probability of progression was 17% in the natalizumab group vs 29% in the placebo group. Furthermore, the addition of natalizumab to β-IFN 1a reduced the risk of disability progression by 24% and annualized relapse rate by 55% over a 2-year period, compared with β-IFN 1a alone.

Currently, natalizumab is recommended for RRMS patients who failed to respond to β-IFN, or RRMS patients with very aggressive disease that may be stabilized with natalizumab first followed by stepping down of therapy to β-IFN or GA. Some patients will develop neutralizing antibodies against natalizumab, which may cause hypersensitivity reactions and loss of drug efficacy over time. Patients reacting to or showing poor response to natalizumab may need testing for anti-
bodies. Importantly, patients treated with natalizumab, especially when preceded by other immunosuppressant therapy or used in combination with β-IFN, rarely develop progressive multifocal leukoencephalopathy (PML) due to latent JC virus infection. The risk of PML related to natalizumab therapy is estimated to be 1 in 10,000 (0.1%) over an 18-month treatment period.24 It is generally accepted that the beneficial effects of natalizumab in active RMS outweigh the risk of PML.24

Mitoxantrone
Mitoxantrone is a synthetic anthracycline with cytotoxic and immunosuppressive effects. It inhibits DNA repair and synthesis in dividing and non-dividing cells by inhibiting DNA topoisomerase II, suppresses T and B cells, induces apoptosis in antigen-presenting cells, and deactivates macrophages.41 A randomized double-blind trial of 194 patients with worsening RMS or SPMS treated with mitoxantrone (5 mg/m² or 12 mg/m²) or placebo 3-monthly for 2 years showed that mitoxantrone offered significant benefits over placebo for the primary outcome, which was a composite of five clinical measures: ambulation index, standard neurological status, change from baseline in EDSS, number of relapses treated with corticosteroids, and time to first time to treat relapse.43

Mitoxantrone provides short-term benefits by reducing relapse rate, development of new cerebral lesions on MRI, and number of patients who experience deterioration of neurological function.44 However, these studies were in a relatively small number of patients, and benefits on disability were not established. Serious potential side effects of mitoxantrone include dose-related impairment of left ventricular ejection fraction and irreversible congestive heart failure when the cumulative lifetime dose exceeds 140 mg/m² (use of mitoxantrone fraction and irreversible congestive heart failure were not established. Most recently, serious side effects of mitoxantrone, including congestive heart failure and therapy-related acute leukemia, are reported to be more frequent than previously believed.24 With the availability of natalizumab, mitoxantrone use is becoming uncommon and less preferred.

Conclusion

DMDs should be considered for RMS patients with active disease, but the timing of therapy initiation and the choice of DMDs should be individualized in view of differences in disease severity, relapse frequency, lifestyles, personal preference and funding support for these expensive therapies.

References


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Physicians often come across patients who complain of frequent headaches. Most have episodic pain, but sometimes the headaches are present on a daily basis. Chronic daily headache (CDH) is a common problem, affecting around 5% of the general population; children as well as adults may be affected. It is not a single entity but a heterogeneous group of disorders, occurring by definition 15 days per month for over 3 months.1,2

Primary headaches refer to disorders that have no clear structural cause and are described as “benign”, but the associated disability can be substantial – depression, anxiety, impaired occupational and physical status. Primary CDH is categorized according to the duration of each episode – whether they last longer or shorter than 4 hours. (Table 1) Some headaches last for only a few seconds or minutes, the most well known of which is trigeminal neuralgia. Others include cluster headache, hypnic headache, paroxysmal hemicrania, primary stabbing headache, and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing syndrome (SUNCT).

Diagnosis

The first step in evaluation is to look for potentially serious pathology. This would be suspected in particular if certain red-flag features are present. (Table 2)

Table 1. Differential diagnosis of primary chronic daily headache

<table>
<thead>
<tr>
<th>Headache duration &gt;4 hours</th>
<th>Headache duration &lt;4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>With autonomic features</td>
<td>With autonomic features</td>
</tr>
<tr>
<td>Chronic migraine</td>
<td>Cluster headache</td>
</tr>
<tr>
<td>Chronic tension-type headache</td>
<td>Paroxysmal hemicrania</td>
</tr>
<tr>
<td>New daily persistent headache</td>
<td>Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing syndrome (SUNCT)</td>
</tr>
<tr>
<td>Hemicrania continua</td>
<td>Without autonomic features</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>Idiopathic stabbing headache</td>
</tr>
</tbody>
</table>

Table 2. Features suggesting a secondary cause of headache

- Systemic illness
- New physical sign
- Sudden onset
- Onset age >40 years
- Progressive worsening of headache
- Worst ever headache
- Headache worsening with cough

Headaches are secondary if attributed to an underlying cause such as tumours, infection or inflammation.

Chronic Migraine

Often, chronic migraine is preceded by a history of episodic migraine, which has increased in frequency over months and years until the patient suffers from daily migraneous or nonmigraneous headaches. The characteristic symptoms such as auras, photophobia, phonophobia and nausea may decrease during this transformation period. Risk factors for migraine transformation include female gender, obesity, frequent headaches at baseline and stressful life events.

Chronic Tension-type Headache

Most patients have bilateral nonthrombing headache without migraine features such as aura, photophobia or nausea. This usually evolves from episodic tension headache and has a pressing or “tightening” quality. The attacks are not aggravated by walking or head movements.

New Daily Persistent Headache

New daily persistent headache (NDPH) is a recently recognized form of primary CDH first described in 1984. It occurs in a person with no past history of headache although this is not an absolute factor. Typically, most patients can recall the exact day on which the pain started, and have experienced daily headache since that time. The diagnostic criteria for NDPH stipulate that pain must be present daily from their point of view, the pain remains “unexplained”. In few other neurological complaints are detailed history and examination as vital because there are no discriminatory laboratory or radiological tests. Once secondary headaches have been excluded, the criteria for primary CDH are clinical and descriptive. The International Headache Society has published a useful but exhaustive classification of headache disorders, which is over 200 pages long plus references, on its website.3
for more than 2 months with a duration of longer than 4 hours a day. The headaches are usually bilateral in location, and are described as throbbing or pressing in quality, with associated symptoms such as nausea, light sensitivity, sound sensitivity, or light-headedness in more than half of the sufferers.

Hemicrania Continua
This is an uncommon condition and is a strictly unilateral headache disorder. The definition as adopted by the most recent 2nd edition of the International Classification of Headache Disorders is in Table 3. It is important to recognize this form of CDH as it can be confused with cluster headache, and treatment for it can be quite effective.

Medication Overuse Headache
All the headache disorders described above can be intensified by the overuse of prescription or over-the-counter analgesics. In fact, the majority of patients who are referred to headache clinics exhibit analgesic overuse. The problem begins with individuals taking one or more drugs to treat headaches over an extended period; this paradoxically leads to more frequent pain and shortening periods between headache recurrence and drug consumption. Patients who consume simple analgesics such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) for ≥15 days per month are at risk of medication overuse headache. The threshold is reduced to ≥10 days for drugs such as ergotamine, triptans and combination drugs.

Treatment
Treatment of CDH is challenging as usually there is no instant solution and sufferers may have consulted many other doctors and healthcare professionals. The objectives of treatment are to reduce the frequency, severity and duration of attacks, to reduce disability, and to improve daily function. A headache diary is advisable to document the frequency of attacks and analgesic consumption. First-line therapy is with advice on behavioural adjustments such as regular exercise, good sleep hygiene, trigger avoidance, stress reduction and a migraine diet. Some patients may obtain relief from psychotherapy or cognitive behaviour therapy, and there is anecdotal success with yoga and meditation. Medication overuse, if present, should be managed by stopping the offending drugs and using transition therapy with other analgesics such as NSAIDs or a short course of steroids. Sometimes inpatient detoxification regimens can be tried, in which the abused drug should be stopped and preventive drugs started along with anxiolytics, antiemetics and rescue therapy.

The mainstay of treatment of CDH is prophylactic drug therapy; most studies have concentrated on tricyclic antidepressants (amitriptyline, nortriptyline), anticonvulsants (valproate, topiramate, gabapentin, pregabalin) and beta-blockers (propranolol, atenolol, metoprolol). Selective serotonin reuptake inhibitors (fluoxetine) are useful in those with associated psychiatric comorbidity. Botulinum toxin is expensive but can lead to marked improvement.

Patients who do not respond to first-line treatment may need multiple prophylactic drugs to control headache attacks. Those with refractory headaches may be referred for specialist assessment for review of the diagnosis (to look for unusual causes such as idiopathic intracranial hypertension and define the type of headache), and for management of chronic pain and medication overuse. Multidisciplinary care is required for patients with psychiatric morbidity and chemical dependency.

References:
Triad of Neuropathic Pain

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