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PARANEOPLASTIC SYNDROMES (F GRAUS, SECTION EDITOR)

Treatment Options in Paraneoplastic Disorders of the Peripheral Nervous System

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Opinion statement

Paraneoplastic disorders of the peripheral nervous system (PNS) are the most frequent manifestation of paraneoplasia. As with the central nervous system, two categories of immune mechanisms are distinguished. On one side, antibodies toward intracellular antigens (HuD and CV2-CRMP5) occur with subacute sensory neuronopathy or sensorimotor neuropathy probably depending on a T cell mediated disorder (group 1). On the other side, the Lambert-Eaton myasthenic syndrome (LEMS) and peripheral nerve hyperexcitability (PNH) occur with antibodies to cell membrane antigens, respectively, the voltage gated calcium channel and CASPR2 proteins, which are responsible for the disease (group 2). Treatment recommendation mostly depends on class IV studies. Three lines of therapeutics can be proposed, namely tumor, immunomodulatory and symptomatic treatments. Cancer treatment is crucial since an early tumor cure is the best way to stabilize patients in group 1 and improve those in group 2. This implies the use of an efficient strategy for cancer diagnosis. With group 2 symptomatic treatment including 3,4 diaminopyridine for LEMS and carbamazepine for PNH may suffice to obtain good quality remission. Immunomodulatory treatments like IVIg and plasma exchange, which have a well-established efficacy in antibody dependent diseases, may be used as second line treatments. Rituximab, for which there is only little evidence in this context, may be kept in a third line for severe refractory patients. With group 1 patients, who frequently develop an evolving and disabling disorder, bolus of methylprednisolone and or IVIg may be recommended while searching for and treating the tumor. If the

tumor is not found and the patient deteriorates, monthly pulses of cyclophosphamide may stabilize the patients. Antidepressants and antiepileptic drugs efficacious in the treatment of neuropathic pain are to be used as symptomatic treatment when necessary. The choice is then based on the cost effectiveness and tolerance of these drugs.

Introduction

Clinically overt peripheral nervous system (PNS) involvement affects up to 15 % of patients with cancer and includes compression or infiltration by the tumor, treatment side effects, nutritional factors, and virus infections [1]. The term of paraneoplastic neurological syndrome is restricted to disorders that are not explained by these mechanisms and concerns less than 1 % of patients [2]. However, in the PNSEuronetwork database, peripheral neuropathy is the most frequent manifestation of paraneoplasia affecting more than one third of paraneoplastic patients [3].

Substantial progress over the past decades has demonstrated that the mechanisms by which paraneoplastic disorders develop are autoimmune. With carcinoma the expression by the tumor of a self-antigen present on the nervous system may lead to a breakdown of immune tolerance and lead to the activation of auto-aggressive B and T cells and the production of auto-antibodies [4, 5]. With lymphoma, the mechanisms are different and involve factors secreted by the tumor including cytokines and, more frequently, a monoclonal immunoglobulin that can behave as an auto-antibody or acquire specific physicochemical properties leading to the formation of amyloid deposits or cryoglobulin precipitates.

Classification of Paraneoplastic Disorders of the PNS

As with central nervous system paraneoplastic disorders, two categories of antigens are now distinguished, namely intracellular and cell surface antigens [6, 7]. This distinction has important consequences since, although antibodies are produced with both types of antigens, they probably do not have access to their target when the antigen is intracellular while T cells are the main effectors of the immune process. The situation is different when the antigen is incorporated in the cell membrane, such as myelin proteins, gangliosides, ion channels or proteins associated to them since a body of evidence now clearly shows that in this case antibodies have access to their target and may modulate the cell surface expression of the protein or damage the cell membrane by complement activation [6, 8]. The practical consequence is that antibody mediated disorders are likely to better respond to immune treatments than cell mediated paraneoplastic diseases. Another important difference is that with intracellular antigens, the immune response is almost universally associated with an underlying tumor, while with surface antigens a cancer may or may not be present [8]. This review is restricted to paraneoplastic PNS disorders involving the mechanisms described above living aside the question of disorders occurring with lymphoma which form a separate question.

Paraneoplastic Disorders of the PNS Associated with Antibodies Toward Intracellular Antigens

Two intracellular antigens are mostly associated with paraneoplastic PNS disorders, namely the HuD and CV2/CRMP5 proteins, while peripheral neuropathy is exceptional with antibodies directed toward other onconeural proteins. HuD is widely expressed in neurons of the central and peripheral nervous system including autonomic neurons [9] but because they are less or not protected by the blood–brain barrier, sensory and autonomic ganglia are mainly affected. Subacute sensory neuropathy (SSN) is the most frequent paraneoplastic disorder and typically occurs with anti-Hu antibodies [3]. Recently published diagnostic criteria and strategy allow the identification of SNN from other sensory neuropathies and among SSN of paraneoplastic forms [10, 11•]. If SSN is the most frequent and usually predominant manifestation of the anti-Hu syndrome it is isolated in only 24 % of patients, the others combining central and peripheral nervous system involvement including lesions of motor neurons [12]. Small cell lung cancer (SCLC) is typically responsible for SSN but other tumors, including breast cancer and Hodgkin's diseases are possible. Up to 15 – 20 % of patients with paraneoplastic SSN may remain seronegative. If SSN is typically a disabling syndrome that can leave the patient bedridden, there are a number of cases with a mild and sometimes indolent course.

In the PNS, the CV2/CRMP5 protein is expressed in sensory neurons and in axons and Schwann cell [13]. The neuropathy of patients with anti-CV2 antibodies is different from that of the anti-Hu syndrome being sensory or sensorimotor in the lower limbs and combines neuronal, axonal and myelin alterations being frequently associated with central nervous system or ocular involvement [14]. SCLC and thymoma are the most frequent associated tumors.

Paraneoplastic Disorders of the PNS Associated with Antibodies Directed Toward Cell Surface Antigens

Two motor and autonomic neuron membrane proteins of the PNS, namely an ion channel and a protein associated to a ion channel are the targets of IgG antibodies in this context.

Antibodies toward the voltage gated calcium channels (VGCC) are responsible for the Lambert-Eaton myasthenic syndrome (LEMS) by blocking calcium entry, a necessary step for acetylcholine release at the presynaptic level [15]. LEMS patients develop an association of motor deficit improved by exercise (potentiation) and cholinergic autonomic system perturbations. In 40 to 60 % of cases, LEMS occur with SCLC [16, 17]. Anti-VGCC antibodies are present in 85 to 90 % of patients and in almost 100 % with cancer [18–20]. Anti-SOX1 antibodies help to distinguish paraneoplastic from non paraneoplastic LEMS [21, 22]. In a subgroup of patients, LEMS or VGCC antibodies occur with paraneoplastic cerebellar degeneration or with the anti-CV2/CRMP5 and anti-Hu syndromes [14, 23]. Therefore, a search for potentiation should be systematically performed in these conditions inasmuch as LEMS improves with treatment.

Antibodies recognizing contactin-associated protein-2 (CASPR2), a protein associated with potassium voltage gated channels (VGKC)[24, 25••] occur with acquired neuromyotonia, peripheral nerve hyperexcitability (PNH), or Isaacs' syndrome, all of them characterized by abnormal muscle activities generated in motor axons [26]. In some patients, PNH is associated with autonomic and/or central nervous system involvement reaching in particular cases the diagnosis of Morvan's syndrome [27]. PNH occurs with thymoma in 15 – 20 % of cases, less frequently with SCLC and occasionally with Hodgkin's disease or plasmocytoma [27]. Dysimmune mechanisms suggesting a direct role of VGKC antibodies have been initially identified [28, 29], but CASPR2 is now known to be the actual immune target even if numerous patients do not have the antibody [25••, 26, 30]. In Morvan's syndrome, the central nervous system involvement is frequently associated with LGI1 antibody which mostly occur with limbic encephalitis [31••, 32••].

Treatment

Owing to the rarity of paraneoplastic PNS disorders good quality controlled studies are difficult to conduct. For this reason, most of the evidences rely and uncontrolled studies or expert opinion (class IV) while class I or II studies are rare. Three categories of treatment can be considered. The first is tumor treatment, the second is immunomodulatory treatment and the last is symptomatic treatment.

Tumor treatment is the best way to stabilize and perhaps occasionally improve paraneoplastic disorders associated with intracellular antigen antibodies (class IV study) [12, 33] while patient with LEMS and PNH usually improve [34]. This is a crucial point since as shown by Fig. 1, in patients with antibodies to intracellular antigens, the inflammatory process and its consequence on neural structures follows an acute monophasic course even though autoantibodies usually persist in the serum, living a therapeutic window that does not exceed a few weeks or months [35]. Therefore, all the efforts should be made to obtain as soon as possible the diagnosis of the tumor and treat it efficiently. With this aim, guidelines have been proposed by the EFNS taskforce specifying the strategy to follow in search of the underlying cancer [36••].

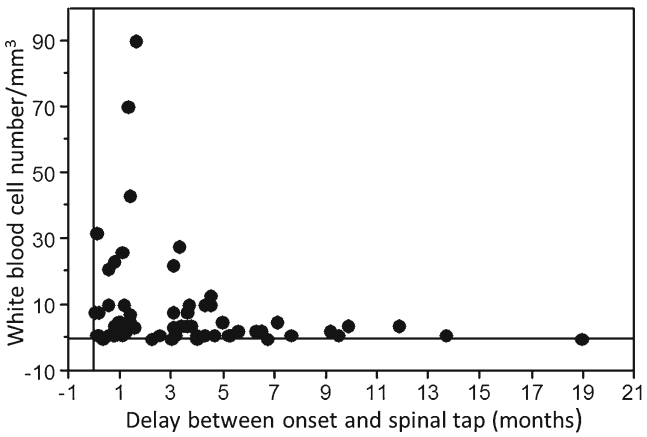

Fig. 1. Distribution of the CSF cell inflammatory reaction according to the delay between the neuropathy onset and the spinal tap in patients with subacute sensory neuropathy originating from the PNSEuronetwork database. Patients investigated within 3 months of the onset of the disorder have a CSF cell reaction which sharply decreases afterward.

Immunomodulatory treatments including prednisolone, intravenous immunoglobulins (IVIg) [37], plasma exchanges [38], cyclophosphamide [39], tacrolimus [40] and rituximab [41] in monotherapy or in combination [42, 43] have been tested in paraneoplastic PNS disorders associated with intracellular antibodies in uncontrolled studies or in trials including different paraneoplastic disorders or antibodies (class IV studies). Their efficacy is not clearly proved although some patients improve particularly those with minor or mild disability and early treatment. Therefore, with anti-Hu or anti-CV2 antibodies, our Reference Center for Paraneoplastic Neurological Syndrome uses to recommend treating patients with an early diagnostic with high dose steroids and/or IVIg when searching for the tumor. Cyclophosphamide can be used as a second line treatment when the cancer is not detected. Clearly controlled studies are necessary and these treatments or drugs that can rapidly block the access of immune cells to the nervous system such as natalizumab need to be investigated in patients with an early diagnostic. In patients with LEMS who do not improve with symptomatic and tumor treatments, IVIg have showed short term efficacy in a small controlled study (class I - II) [44] and plasma exchanges in a class IV study [45]. Rituximab in a class IV study improved refractory patients with LEMS [46].

Symptomatic treatments are recommended in the management of paraneoplastic patients [34]. Although there is no trial on neuropathic pain, a potentially disabling symptom in SSN, drugs that have known efficacy from class I studies in other neuropathies such as amitriptyline, duloxetine, venlafaxine, gabapentin or pregabalin may be used in SNN as first line treatment and tramadol and opioids which are recommended as second line treatment can be used in the same condition [47•]. Small class I studies [48–51] confirmed by a meta-analysis[52••] have showed that LEMS improves with 3–4 diaminopyridine which is now the first line recommended treatment [52••]. In PNH antiepileptic drugs and particularly carbamazepine may reduce muscle overactivity (Class III studies) [53•].

There is today no validated therapeutic strategy in patients with paraneoplastic PNS disorders. However, using the results mentioned above the strategy exemplified in Figs. 2 and 3 may be proposed which is based on the one used in the French Reference Center for Paraneoplastic Neurological Syndrome.

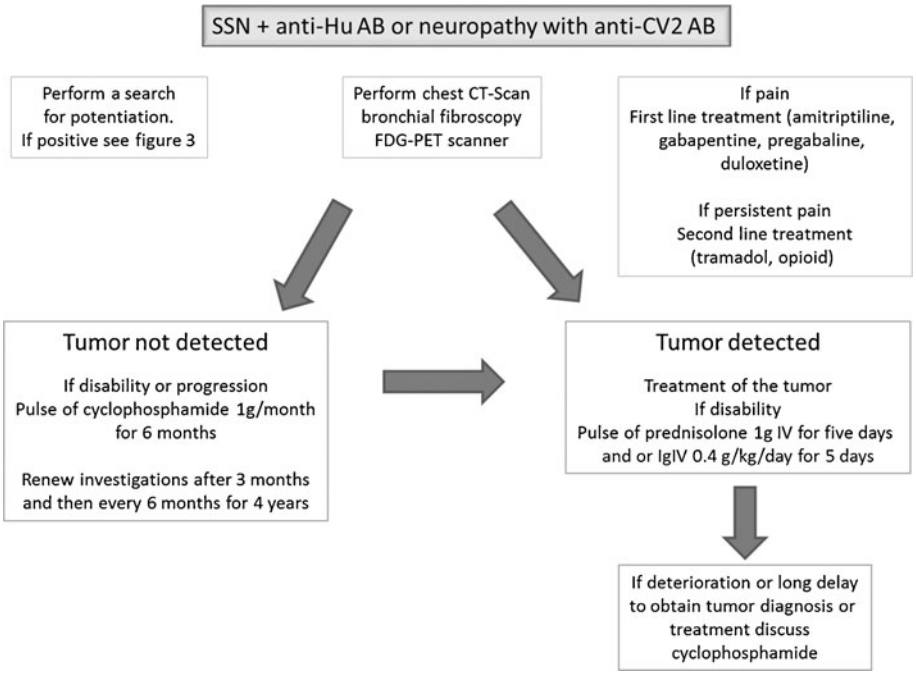

Fig. 2. Proposed strategy for the management and treatment of patients with peripheral neuropathy and anti-Hu or CV2/CRMP5 antibodies. AB: antibody. FDG: fluorodesoxyglucose. IV: intravenous. Ig: immunoglobulin. G: gram. Kg: kilogram.

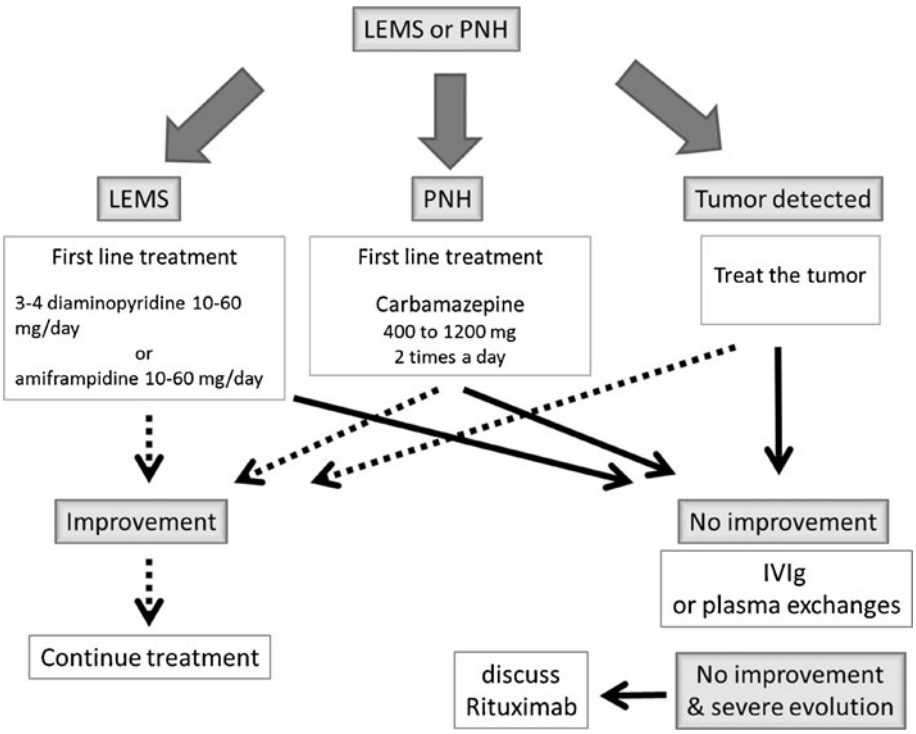

Fig. 3. Proposed strategy for the management of Lambert-Eaton myasthenic syndrome (LEMS) and peripheral nerve hyperexcitability (PNH). Mg: milligram. IVIg: intravenous immunoglobulin.

Pharmacologic Treatment

Immunosuppressant and Immunomodulatory Treatments

Pulse of Methylprednisolone (MP)

	Methylprednisolone is a synthetic glucocorticoid which has a wide range of effects including changes to metabolism and inflammatory and immune responses. Pulses of MP have a demonstrated efficacy in attack treatment of severe manifestations of systemic lupus erythematosus and rheumatoid arthritis, necrotizing vasculitis, graft rejection or graft versus host disease. It is a well-known treatment of relapse in multiple sclerosis.
Standard dosage	There is no standardized protocol of MP administration in the treatment of paraneoplastic disorders of the PNS. In the well-established indications, standard dosage varies from 500 to 1000 mg/day intravenously for 3 to 5 days. At least 1000 mg for 3 days may be recommended in paraneoplastic disorders.
Contraindications	Hypersensitivity to MP, ongoing sepsis, uncontrolled psychosis, evolving viral infection (hepatitis and herpes virus).
Main drug interactions	Treatments able to induce wave burst arrhythmia should be avoided during pulses of MP administration. The metabolism of several drugs such as aspirin, oral anticoagulants, heparin, digitalic and antiepileptic treatments may be modified.
Main side effects	Tachycardia, cardiac arrhythmia, hypokalemia, hyperglycemia, gastric ulcer, acne, insomnia, euphoria, sometimes confusion, maniac state or seizure.
Special points	In certain conditions pulses of MP may be combined with infusion of IVIg or cyclophosphamide.
Cost / cost effectiveness	Inexpensive. Cost effectiveness has not been studied in this context.

Cyclophosphamide

	Cyclophosphamide is an alkylating agent commonly used in anticancer chemotherapy and as an immunosuppressant in autoimmune diseases.
Standard dosage	There is no standardized protocol for cyclophosphamide administration in the treatment of paraneoplastic disorders of the PNS. We use 1 gram intravenously administered over one day every four weeks according to the procedure described in Fig. 2. An alternative posology may be 600 mg/m2 of body surface.
Contraindications	Hypersensitivity to cyclophosphamide • Absolute contraindications: severe blood marrow insufficiency. Ongoing sepsis. Urinary infection. Antecedent of hemorrhagic cystitis. Pregnancy and breast-feeding. Treatment with phenytoin and recent yellow fever vaccination. • Relative: live vaccines.
Main drug interactions	Phenytoin, live vaccine. Possible interaction with warfarin and other anti-vitamin K treatments.
Main side effects	Nausea, transient neutropenia or thrombopenia, transient alopecia, amenorrhea, azoospermy. Hemorrhagic cystitis. With high cumulative

	doses there is a risk of cancer development years after the end of treatment. Rarely, cardiomyopathy and interstitial pneumopathy may occur.
Special points	Because of the risk of hemorrhagic cystitis it is recommended to systematically associate mesna 600 mg (or 60 % of the total dose of cyclophosphamide) intravenously distributed before and after the infusion of cyclophosphamide.
Cost / cost effectiveness	Inexpensive. Cost effectiveness has not been studied in this context.

Intravenous Immunoglobulins (IVIg)

	Intravenous immunoglobulins have a large spectrum of immunomodulatory effects and have showed efficacy in a wide spectrum of autoimmune neurological diseases [54].
Standard dosage	There is no standardized protocol of treatment with IVIg in paraneoplastic disorders. The one commonly used is that of the treatment of idiopathic thrombopenic purpura, namely 0.4 grams/kilogram of body weight for 5 days (total dose of 2 gram/kilogram). If an improvement is obtained and then the neurological status deteriorates after a few weeks despite tumor treatment, infusion of IVIg may be renewed every 4 weeks.
Contraindications	Hypersensitivity to immunoglobulins.
Main drug interactions	None
Main side effects	Shivers and fever, headache, aseptic meningitis, eczema. More rarely, hemolytic anemia, acute renal failure, deep vein or arterial thrombosis and anaphylactic reaction in patients with deficit in IgA may occur. IVIg are stable blood-derived products. Although manufacturers use sophisticated methods to eliminate the known conventional and non-conventional infectious agents including prions a low risk of transmission of an as yet unknown agent cannot completely be ruled out.
Special points	A dosage of serum IgA is recommended before the first infusion. In case of deficit, solution of immunoglobulins depleted in IgA must be used. In patients with chronic renal failure or in elderly the expected benefice of the treatment must be evaluated and a rehydration of the patient with saline solution may be recommended prior to the infusion.
Cost / cost effectiveness	Expensive. Cost effectiveness of IVIg has not been studied in this context.

Rituximab

	Rituximab is a chimeric monoclonal antibody against CD20, a protein primarily found on the surface of B cells. It is used to treat diseases characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells including lymphomas, leukemias, transplant rejection, and some autoimmune disorders. The immunomodulatory action of rituximab on B cells is not limited to the reduction of autoantibody producing plasma cells but probably involves a wide range of actions on the immunoregulatory function of these cells [55].
Standard dosage	There is no validated dosage of rituximab in paraneoplastic PNS syndrome. The most frequently used protocol in lymphoma and in autoimmune diseases is 375 mg/m^2 of body surface every week for four weeks [55, 56].

Contraindications Hypersensitivity to rituximab. Ongoing bacterial or viral infection. Live vaccine injection. Cardiac failure. Abnormal blood cell count.

Main drug interactions Live vaccines. Immunosuppressant increasing the risk of immunodepression. Increased renal toxicity in patients with high tumor burden receiving platinum salts.

Main side effects

- Deaths within 24 hours of rituximab infusion have been reported. These fatal reactions usually occurred after the first infusion and were due to a reaction complex including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock.
- Tumor lysis syndrome with acute renal failure requiring dialysis with instances of fatal outcome has been reported in patients with lymphoma and a high tumor burden.
- Severe mucocutaneous reactions, some with fatal outcome.
- More frequently mildly to moderately severe hypersensitivity reaction at the first infusion including fever, shiver, headache, myalgia, hypotension, bronchospasm, and angioedema. These reactions justify a systematic preventive treatment before the infusion associating intravenous corticosteroids, antihistaminic and paracetamol.
- Several cases of multifocal progressive leucoencephalopathy have been reported in patients treated with rituximab for systemic lupus erythematosus and other autoimmune diseases and who have received prior immunosuppressive treatments [57].

Special points If there is several lines of evidence arguing that rituximab is a choice treatment in paraneoplastic disorders of the central nervous system due to anti-cell surface antibodies and especially NMDA-R antibodies [41, 58, 59], evidence is far less compelling with PNS disorders and rely on two uncontrolled studies. The first is an unblinded trial in which nine patients with anti-Hu or anti-Yo associated paraneoplastic neurological syndromes received a maximum of four monthly intravenously administered infusions of rituximab (375 mg/m^2). Three patients improved by at least one point on the Rankin Scale [46]. In the other study, three patients with LEMS treated openly in the UK with rituximab were collected from referring physicians, with full case ascertainment and follow-up. All of them were reported to have improved [46]. Therefore, at present, rituximab should probably be used as a third line treatment in patients with cell membrane antibodies (LEMNS-PNH) who fail to respond to symptomatic treatments and IVIg or plasma exchange.

Cost / cost effectiveness Expensive. Cost effectiveness of rituximab as not been studied in paraneoplastic disorders.

Symptomatic Treatments

3–4 Diaminopiridine (3,4 DAP)/Amifampridine (AFPD)

3,4-Diaminopyridine blocks potassium channel efflux in nerve terminals thereby increasing the duration of action potentials. This allows Ca2+

	channels to stay open for a longer time leading to a greater acetylcholine release in the synaptic cleft. Therefore, 3,4 DAP is the recommended first line treatment in LEMS [52••].
Standard dosage	3,4-DAP up to 10–20 mg three times a day / AFDP up to 10–20 mg, three times a day, tablets to take by mouth. The average dose is 40 mg/day.
Contraindications	Hypersensitivity to 3,4 DAP or AFPD, epilepsia, uncontrolled asthma, concomitant treatment by sultopride, treatment known to prolong QT interval, patient with congenital QT interval prolongation, pregnancy and breath feeding. These treatments must be used with caution in patient with renal or hepatic insufficiency (slow titration and low dose) or association with a treatment known to lower the seizure threshold.
Main drug interactions	Sultopride.
Main side effects	Treatment is usually well tolerated. Perioral tingling and digital paresthesiae, transient vertigo, insomnia, epigastric discomfort are the more frequent side effects. Seizures are the most severe dose dependent but rare side effect and usually occur beyond 60 mg/day. QT interval prolongation is possible. Supraventricular tachycardia has been reported with iatrogenic or voluntary intoxication. According to the small size of the treated population, the frequency of side effects is not precisely known.
Special points	None.
Cost / cost effectiveness	3,4-DAP as an unlicensed formulation which average dose is 40 mg a day yearly costs 730 L per patient in UK. The more recent salt formulation of 3,4-DAP namely AFPD for the same average dose yearly cost 29448 L [52••].

Carbamazepine

	Carbamazepine is typically used for the treatment of seizure disorders and neuropathic pain. It may be used as a second line treatment for bipolar disorder. Carbamazepine stabilizes the inactivated state of voltage-gated sodium channels and thereby reduces neuron and axon excitability. This is the reason why it is a choice drug in PNH.
Standard dosage	400–1200 mg a day.
Contraindications	Hypersensitivity to carbamazepine, atrioventricular block, bone marrow aplasia or history of bone marrow aplasia, acute porphyria. Use with caution in case of glaucoma, prostate adenoma, hepatic, cardiac or renal insufficiency and in elderly persons.
Main drug interactions	Carbamazepine must not be associated to saquinavir. Possibility of pharmacologic interaction with oral contraceptives, clozapine, erythromycin, isoniazid, ritonavir, tramadol, dextropropoxiphene, lithium salts, valpromide, and warfarin.
Main side effects	Minor to moderate: drowsiness, dizziness, unsteadiness, nausea, vomiting, headache, anxiety, memory problems, diarrhea, constipation, heartburn, dry mouth, back pain, chest pain, yellowing of the skin or eyes, vision problems. More severe: confusion, loss of contact with reality, cutaneous allergic reaction, allergy, lymphopenia, thrombosis, hyponatremia, liver enzyme elevation, hepatitis, cardiac dysrhythmia.
Special points	Health care professionals should be aware that dangerous or even fatal skin reactions (Stevens–Johnson syndrome and toxic epidermal necrolysis) may occur with carbamazepine.

Cost / cost effectiveness Inexpensive. In the treatment of neuropathic pain, carbamazepine, after amitriptyline, is the most cost-effective treatment.

First Line Treatment of Pain

Specific drugs According to the EFNS guidelines [47•], antidepressants can be used as first line treatment of neuropathic pain in peripheral neuropathy. This includes tricyclics, especially amitriptyline, and the selective serotonin reuptake inhibitors (SSRI) duloxetine and venlafaxine. The antiepileptics gabapentin and pregabalin are recommended in the same conditions.

Standard dosage Amitriptyline: 50–150 mg/day; duloxetine: 60–120 mg/day; venlafaxine extended-release 75–225 mg/day; pregabalin: 150–600 mg/day; gabapentin: 1,200 – 3,600 mg/day.

Contraindications Hypersensitivity to these drugs.

- Amitriptyline: closed-angle glaucoma, non-selective monoamine oxidase inhibitors (MAOI), sultopride.
- Duloxetine: non-selective MAOI, fluvoxamine, ciprofloxacin and enoxacin, severe blood hypertension.
- Venlafaxine: non-selective MAOI.
- Gabapentin: none
- Progabalin: none

Main drug interactions

- Amitriptyline: alcohol, clonidine, selective MAOI A, linezolid, adrenaline, SSRI, and thioridazine.
- Duloxetine: alcohol, selective MAOI A, SSRI and drugs metabolized by CYP2D6 including risperidone and tricyclic antidepressants. Anticoagulants and platelet antiaggregants.
- Venlafaxine: selective MAOI, SSRI, tryptans, lithium, tramadol, Hypericum perforatum, tryptophan and alcohol.
- Gabapentin: morphine.
- Progabalin: alcohol, lorazepam,

Main side effects

- Amitriptyline: frequent: mouth dryness, constipation, somnolence, blurring vision, dysuria and urine retention, weight gain. Rarely: tremor, seizure and occasionally: toxic hepatitis and hematologic perturbations. Increased risk of suicide in cases of depression.
- Duloxetine: nausea, somnolence, dry mouth, constipation, diarrhea, hyperhidrosis and dizziness. Duloxetine induces little cardiovascular side effects. Rare cases of hepatotoxicity have been reported. Increased risk of suicide in case of depression.
- Venlafaxine: frequent: mouth dryness, constipation, somnolence, dizziness, blurring vision, nausea, sexual dysfunction. Rarely: pulmonary hypertension (class effect), tachycardia, blood hypertension, miscarriage and congenital malformation so that contraception is recommended when appropriate. Increased risk of suicide in cases of depression.

- Gabapentin: somnolence, dizziness, tremor, dysarthria, weight-gain, peripheral edema, increased depression and suicide risk, and rarely hepatotoxicity.
- Progabalin: dizziness, drowsiness, dry mouth, edema, blurred vision, weight gain, and difficulty concentrating. Other side effects include reduced blood platelet counts, and increased blood, increased depression and suicide risk.

Special points All of these treatments need a progressive titration to avoid the most frequent side effects and determine the appropriate dosage which may vary greatly from patient to patient. Association of drugs of the same class must be avoided.

Cost and cost effectiveness Studies have showed that tricyclics are the most cost effective treatment in neuropathic pain [60]. Amitriptyline: inexpensive. Gabapentin: moderate. Progabalin: expensive. Venlafaxine: expensive. Duloxetine: expensive.

Other Treatment

Plasma Exchanges

Plasma exchange is a standard treatment for many diseases including Guillain-Barré Syndrome [61], chronic inflammatory demyelinating polyneuropathy [62], and myasthenia gravis [63]. Plasma exchange offers the quickest short-term answer to remove circulating autoantibodies and proinflammatory cytokines.

Standard procedure As in other neurological diseases, there is no standard procedure for plasma exchange in paraneoplastic PNS disorders. Different methods (discontinuous or continuous flow centrifugation), number of exchanges and total plasma volume exchanged can be used. The replacement fluid is albumin or mixture of albumin and saline. At least two plasma exchanges per week for 2 to 4 weeks may be performed to check their effectiveness.

Contraindications Hypersensitivity to albumin or other products used for the exchange.

Complications Bleeding or hematoma at catheter insertion, catheter infection, citrate induced hypocalcemia. Hypotension, fatigue, anemia, thrombopenia, risk of transfusion reactions or as with IVIg transfusion transmitted diseases.

Special points None

Cost / cost effectiveness Expensive. Cost effectiveness has not been studied in paraneoplastic disorders.

Disclosure

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Dr. Camdessanche reported no potential conflicts of interest relevant to this article.

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- •• Of major importance

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