THERAPEUTIC FOCUS - Direct Effects (TM) Diabetic Neuropathy Therapy: Treating Symptoms & Modifying Disease

INTRODUCTION

Peripheral neuropathy is the most common neurological manifestation of diabetes. Symptoms of diabetic peripheral neuropathy (DPN) often manifest before diagnosis of diabetes. Most common symptoms are numbness of feet with tingling, burning, and aching sensations. As it progresses, fingers and hands become affected in symmetric fashion. DPN may affect 50% to 90% of diabetics, depending on criteria used. With obesity in epidemic proportion, insulin resistance with incidence of diabetes has significantly increased.

In addition to persistent neuropathic symptoms affecting sleep, wearing shoes and socks, and walking; most significant is loss of protective sensation in feet. As sensation is lost, minor injuries are undetected and not addressed early; leading to ulcerations, infection, and potential amputation. Between 60% to 70% of foot ulcers are preceded by neuropathy. And 85% of diabetes-related lower limb amputations are preceded by foot ulcer. Three of 10 undergoing lower limb amputation will lose another leg within 3 years, with over half dying within 5 years of first amputation. With such grim statistics, it makes sense to treat DPN when detected to modify disease and control symptoms.

THE ETIOLOGY OF DPN & TREATMENT CONSIDERATIONS

The cause of nerve damage in DPN is loss of blood flow to small peripheral nerves and cutaneous nerve-endings, result of blockage of small capillaries (vaso nervorum) by metabolic process of diabetes (Figure 1). Ultimately, as diabetes progresses, other blood vessels, such as to heart and brain, are affected, leading to heart attacks and strokes.



As blood flow and nutrients are lost, nerves are unable to function properly or die, causing loss of sensation with neuropathic symptoms of tingling, burning, sharp pain, electric-like sensations, and pain to touching clothes and bed sheets (allodynia). Part of pathologic process is loss of myelin (demyelination) of peripheral nerves that prevents proper nerve conduction and results in neural "short-circuiting and cross-talk," causing neuropathic symptoms. Demyelinated nerves leak potassium, further affecting conduction. Accordingly, drugs that block potassium channels, such as 4-amino pyridine (4-AP), can improve conduction in damaged nerves. One such oral extended-release preparation, Ampyra (Acorda Therapeutics) is indicated for improving nerve conduction in multiple sclerosis (MS), an immune-based central demyelinating process.

Systemic treatment for peripheral demyelinating neuropathic process, such as DPN, must consider coexisting peripheral vascular disease, limiting drug access to damaged nerves. In this regard, it makes sense to use topical preparations of drug compounded to allow penetration to the level of cutaneous nerve endings, an area of pathologic process in DPN. Additional issues of systemic therapy complicating drug delivery to peripheral nerves include the following (Figure 2):

-GI transit and absorption

-Hepatic first-pass metabolism

-Cardiac and hemodynamic factors affecting drug delivery and blood levels

-Drug interactions with concomitant medications

-Side effects from drug action at unintended areas



NEUROTROPHIC SUPPORT TO ENHANCE BLOOD FLOW & IMPROVE PERIPHERAL NERVE FUNCTION

In addition to control of blood sugar levels through medications, diet, and exercise, specific nutritional agents help heal damaged nerves in DPN. One product is METANX® (Pam Labs), a combination of L-Methylfolate 3 mg, Methylcobalamin 2 mg, and Pyridoxal 5'–phosphate 35 mg. It is considered "Medical Food" and regulated by the FDA with prescription requirement. Metanx addresses underlying conditions of endothelial dysfunction in blood vessels to small nerves (vaso nervorum) that leads to DPN.

L-methyl folate increases nitric oxide synthesis, which improves blood flow to cutaneous nerves. Metanx is prescribed as a twicedaily tablet.

Studies with oral L-Methylfolate, Methylcobalamin (Me-Cbl), and Pyridoxal 5' - phosphate (P-5-P) in DPN indicate improvement of cutaneous sensation at feet of affected patients compared to baseline at 6 months and 1-year therapy.

A preliminary study also suggests LMethylfolate, Me-Cbl, and P-5-P are associated with increased intraepidermal nerve fibers density (IENFD) in patients with DPN. The increased epidermal nerve fiber density may be associated with diminished symptoms of pain, anesthesia, paresthesia, and dysesthesia observed with therapy.

A skin biopsy is performed to measure IENFD in lower extremities of patients with DPN. Loss of nerve fibers is associated with increased neuropathic pain. Small Fiber Neuropathy (SFN) is a major cause of painful burning, numbness, and tingling in feet and hands of DPN and other neuropathic conditions. SFN often precedes diagnosis of diabetes and has been termed "impaired glucose tolerance neuropathy."

Diagnostic efficiency of skin biopsy is $\approx 88\%$, making it useful in diagnosing SFN associated with diabetes. The test is invasive, but enables direct study of small nerve fibers. Often in patients with DPN who still only have SFN, routine nerve conduction studies and electromyography are typically normal as these only measure large nerve fiber function (Figure 3).

FIGURE 3

Cutaneous Free Nerve-Endings: Site of Direct Effects™Topical DPN Therapy



SYMPTOMATIC PHARMACOLOGICAL TREATMENTS FOR DPN & OTHER NEUROPATHIES

There exist numerous drugs to treat symptoms of DPN but which do not affect underlying condition causing peripheral nerve dysfunction. They do not disease modify or repair nerves. Among symptomatic therapies for DPN and other peripheral neuropathies are:

-"Pain pills," such as narcotics, NSAIDs, and acetaminophen -Tricyclic antidepressants, such as amitriptylene (Elavil) -SNRIs, such as venlafaxine (Effexor), duloxetine (Cymbalta), and milnacipran (Savella)

-Anticonvulsants gabapentin (Neurontin) and pregabalin (Lyrica) -Topical products lidocaine cream and patch anesthetize skin to provide neuropathic pain relief but make affected areas more numb

-Capsaicin cream causes initial increased burning sensation followed by temporary relief

UNMET NEED IN DPN & TOPICAL COMPOUNDED CREAMS AS "LOGICAL POLYPHARMACY"

There exists a void in treatment of DPN. As SFN and DPN are primarily conditions affecting cutaneous (skin) nerves and free nerve-endings, the author has developed a topical therapy for treating DPN and other neuropathies that manifest similar peripheral nerve dysfunction. Compounded combination cream is rubbed into the dorsum and soles or palms (top and bottom) of affected feet and hands two to three times/day (Figure 4).



Compounded cream consists of generic drugs commonly used to treat neuropathic pain in combination with L-methyl folate, methyl cobalamin, and 5-pyridoxal phosphate. Additionally, 4-amino pyridine (4-AP) and apomorphine (Apo) are added to improve conduction of damaged nerves and enhance treatment of neuropathic symptoms. Other compounds and vitamins are added according to need, as discussed further.

4-Amino Pyridine (4-AP)

4-Amino pyridine, 4-AP (fampridine, dalfampridine) is an organic compound with the chemical formula C5H4N-NH2. 4-AP extended-release tablet, name brand AMPYRA (dalfampridine), was granted orphan drug status in 2010 to improve walking in patients with multiple sclerosis, MS. 4-AP is a potassium channel blocker demonstrated to increase walking speed in MS, which has also been shown to improve visual function, enhance motor skills, and relieve fatigue in MS. Common 4-AP side effects include dizziness, nervousness, nausea, and other GI symptoms. Overdoses can cause paresthesias, seizures, and heart rhythm disturbances such as atrial fibrillation. 4-AP works through potassium channel blockade. Electrophysiologic studies of demyelinated axons show augmented potassium currents increase extracellular potassium ion concentration, decreasing action potential duration and amplitude. This may cause nerve conduction failure. Potassium channel blockade apparently reverses this effect. Studies have shown 4-AP, as a potent calcium channel activator, can improve synaptic and neuromuscular function through direct effect on calcium channel beta subunit of impaired nerves. Although it improves MS symptoms caused by damaged poorly conducting nerves, 4-AP does not prevent MS disease progression.

Spinal cord injury patients have also been observed to improve with 4-AP therapy. These include improved sensory, motor, and pulmonary functions as well as decreased spasticity and pain. Based on the aforementioned and and author's experience with topical 4-AP, improvement in neurological function in MS, stroke, and cerebral palsy patients was seen when applied to back of the neck at hairline (BONATH), nuchal region. It was tried and found useful in treating nerve dysfunction associated with DPN, SFN, and other peripheral neuropathies (Figure 5).



Apomorphine (Apo) & Other Compounds

Apomorphine is used as injection to treat symptoms of Parkinson's disease (PD). The author has extensive experience (USPTO No. 8,592,424,B2, granted November 26, 2013) with it as topical preparation in Parkinson's, tremor, spasticity, erectile dysfunction, and neuropathic pain. Applied to BONATH in PD, motor as well as "nonmotor" PD symptoms were alleviated. Through action at dopamine, serotonin, and norepinephrine receptors, significant pain relieving and muscle relaxant effects are also noted when topically applied to spine and peripheral areas of nerve dysfunction. Adding Apo provides added therapeutic benefit to topical DPN treatment.

Gabapentin and pregabalin are used to treat neuropathic pain of various etiologies, including DPN, post-herpetic neuralgia, spinal radiculopathy, and post-laminectomy syndrome. Local anesthetics, such as lidocaine and prilocaine, are useful as topical treatments in reducing nerve pain, but increase numbness associated with DPN.

Capsaicin, tizanidine, and tramadol are other compounds effective in combination neuropathic creams, depending on patient need. Capsaicin deactivates pain producing free nerve endings through action on TRPV1 receptors on the surface of nerve endings; but can cause significant initial burning. Tizanidine acts as both pain-modulating agent and muscle relaxant. Tramadol, a non-narcotic opioid agonist, provides greater degree of pain relief when needed.

Neuro-Affective Effect of Topical Drugs on Cutaneous Nerve Endings

Finally, topical therapy not only allows active drug to easily and directly reach targeted cutaneous nerve endings without requiring circuitous compromised blood flow, but receptors on nerve endings provide direct neural therapeutic avenue for topically applied neuro-active drugs.

Cutaneous nerve endings are peripheral end-components of dorsal root ganglia with extracellular surface receptors conducive to binding by topically applied drugs. The neurochemical effects of topical agonist and antagonist compounds on endogenous surface receptors may modulate afferent input to dorsal root ganglia, influencing nerve signal processing to brain. Therapeutic benefit appears to be achieved through attenuation of central nervous system (CNS) efferents, as reduction in clinical symptoms. Among cell surface receptors on cutaneous nerve endings are those to TRPV1, NGF (nerve growth factor), opioids/ endorphins; and to endogenous agonists serotonin, dopamine, norepinephrine, and others. It is believed these receptors are affected by topical compounds possessing agonist and antagonist properties, thereby providing therapeutic benefit. CNS and skin are derived from the same embryological tissue, neuroectoderm. Receptors in CNS are therefore represented on skin nerve endings, allowing the two entities to process and share neural information as a closed-loop system (Figure 6).



CONCLUSION

Using the aforementioned methodology, symptomatic and neural restorative therapies treat DPN in preparations applied directly to areas of pathology. The epidermal nerve fiber layer is the target site. As high concentrations of drugs and neurotrophic agents are achieved at places of nerve and blood vessel dysfunction, therapeutic benefit is obtained in much shorter time than through blood flow.

Relief of pain and neuropathic symptoms is typically noted within 5 to 8 minutes of topical drug application. Visible trophic changes in skin occurs within 15 minutes as nerve function is improved and blood flow is redirected in skin and subcutaneous tissue. Improved sensation from pretreatment baseline follows within 30 minutes.

Figure 7 gives examples of results in patients treated with various combinations of drugs and neurotrophic agents. DPN is the most common condition treated but other neuropathies also responded to topical therapy: hereditary neuropathy (Charcot Marie Tooth, chemotherapy related neuropathy, post-traumatic and compression neuropathy, radiculopathy, and metabolic neuropathies.

FIGURE 7

TREATMENT OF PERIPHERAL NEUROPATHY WITH TOPICAL DRUG AND NEUROTROPHIC* COMBINATION CREAMS

Patient	Diagnosis	Duration of symptoms	Treatment	Results
M.M. 67y/o fema	Idiopathic peripheral neuropathy: ? thyroid disease	3 years of numbness, pain, and tingling. 50% decreased sensation bilateral feet.	topical 4-AP, apomorphine, and MFP to left foot.	Left foot sensation improved to 10% decrease from normal in 15 min.
J.M. 69y/o fema	le peripheral neuropathy, chemotherapy post-lumber laminectomy.	pain, numbness, and weakness x 2007, worse after chemotherapy for breast cancer 2009.	4-AP, apomorphine, tramadol topical cream with oral MFP	peripheral neuropathic symptoms stable with improvement of numbness from chemotherapy.
C.M. 75y/o fema	Diabetic peripheral neuropathy	3-4 years bilateral foot numbness, tingling, and pain:L>R.	4-amino pyridine and apomorphine topical cream.	50% reduction in tingling with improved sensation in 10–15 minutes.
M.A. 90y/o fema	familial peripheral neuropathy and failed back syndrome	peripheral neuropathy diagnosed at Mayo Clinic 1995 with EMG/NCV.	2+ years (7/2011) of daily Rx with apomorphine and tramadol cream 2x/d.	With oral tramadol and topical neuropathy cream, able to function normally.
A.M. 72y/o mal	e Diabetic peripheral neuropathy	several years numbness and burning pain with insomnia. Treated with other topical preparations in evening.	combination topical 4-AP, apomorphine, and MFP both feet.	In 5 minutes, improved sensation and pain reduction in both feet. Now using regularly.
	*MFP n	eurotrophic support: methylcobala	min, methyl folate, ar	nd pyridoxal phosphate
R.H. 85y/o male	*MFP n acute metabolic neuropathy superimposed on hereditary CMT neuropathy	Eurotrophic support: methylcobala Life-long with recent worsening to extent could not ambulate without walker	6 weeks Rx of topical 4-AP, apomorphine, gabapentin, lidocaine, prilocaine, and MFP* 3x/day.	Pain, numbness and weakness improved. Ambulating without walker or assistance
R.H. 85y/o male P.D. 87y/o female	acute metabolic neuropathy superimposed on hereditary CMT neuropathy Charcot-Marie- Tooth with recent increased symptoms	Life-long with recent worsening to extent could not ambulate without walker 3 years of increasing pain, numbness, and weakness with gait difficulties.	6 weeks Rx of topical 4-AP, apomorphine, gabapentin, lidocaine, prilocaine, and MFP* 3x/day. 3 weeks of Rx of above combination 2x/ day.	Pain, numbness and weakness improved. Ambulating without walker or assistance 20% improvement in baseline pinprick and temperature; no change in vibratory sensation.
R.H. 85y/o male P.D. 87y/o female K.M. 64y/o male	acute metabolic neuropathy superimposed on hereditary CMT neuropathy CMT neuropathy CMT neuropathy CMT neuropathy Charcot-Marie- Tooth with recent increased symptoms diabetic/ metabolic peripheral neuropathy with superimposed lumbar radiculopathy	Life-long with recent worsening to extent could not ambulate without walker 3 years of increasing pain, numbness, and weakness with gait difficulties. 2 years of numbness, tingling, aching feet with restless legs and sleep disturbance	6 weeks Rx of topical 4-AP, apomorphine, gabapentin, lidocaine, and MFP* 3x/day. 3 weeks of Rx of above combination 2x/ day. 2 weeks of above topical Rx nightly.	 Pain, numbness and weakness improved. Ambulating without walker or assistance 20% improvement in baseline pinprick and temperature; no change in vibratory sensation. 80% relief of pain with 20-30% improvement in sensation within 5-8 minutes of each application. Improved sleep.

Longest continuous treatment period using topical creams for a neuropathic process is more than 3 years. Patient achieved benefit with daily use, symptoms exacerbating when treatment is interrupted. Many peripheral neuropathies are progressive and not curable. In these, treatment relieves symptoms and improves aspects of nerve and vascular function, but rarely normalizes the condition. After diabetes, thyroid disease, B12 deficiency, gammopathies, and other potential causes of peripheral neuropathies remain idiopathic, of unknown etiology.

To view this issue and all back issues online, please visit <u>www.drug-dev.com</u>.

REFERENCES

1. Aung-Din R. Nuchal topical neuro-affective therapy: a novel treatment for Parkinson's disease using apomorphine. Drug Development & Delivery. 2010;10(8):48-54.

2. Aung-Din R. Topical regional neuro-affective (TRNA) therapy: novel ground-breaking triptan drug delivery for treating migraines. Drug Development & Delivery. 2009;9(9):44-51.

3. Boulton A, JM. Management of diabetic peripheral neuropathy. Clinical Diabetes. 2005;23(1):9-15.

4. Boykin JV Jr. Ischemic vascular disease, nitric oxide deficiency, and impaired wound healing. Vascular Disease Management. 2007;2(1):1-8.

5. Gordois A, et al. The health care costs of diabetic peripheral neuropathy in the US. Diabetes Care. 2003;26(6):1790-1795.

6. Laczy B, Cseh J, Mohás M, et al. Effects of pentoxifylline and pentosan polysulphate combination therapy on diabetic neuropathy in type 2 diabetes mellitus. Acta Diabetologica. 2009;46(2):105-111.

7. Marks JB. The forgotten complication. Clinical Diabetes. 2005;23(1):3-4.

8. Partanen J, et al. Natural history of peripheral neuropathy in patients with non-Insulin-dependent diabetes mellitus. N Eng J Med. 1995;333:89-94.

9. Rosenstock J, et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain. 2004;110(3):628–638.

10. Stroes E, van Faasen E, et al. Folic acid reverts dysfunction of endothelial nitric oxide synthase. Circ Res. 2000;86:1129-1134.

11. Van Etten RW, deKoning EJP, Verhaar MC, et al. Impaired NO-dependent vasodilation in patients with type II (non-insulin-dependent) diabetes mellitus is restored by acute administration of folate. Acta Diabetologia. 2002;45:1004-1010.

12. Veves A, Akbari CM, Primavera J, et al. Endothelial dysfunction and the expression of endothelias nitric oxide synthetase in diabetic neuropathy, vascular disease, and foot ulceration. Diabetes. 1998;47:457-463.

13. Walker MJ Jr, Morris LM. Increased cutaneous sensibility in patients with diabetic neuropathy utilizing a pharmacological approach-clinical case evidence: clinical case update. Vascular Disease Management. 2007;2(1):1-8.

14. Ziegler D, et al. Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoic acid. Acta Diabetologia 1995;38(12):1425-1433.

15. METANX[®] Package Insert, Pamlab, L.L.C. Covington, LA 70433, Revised 2/10.



Dr. Ronald Aung-Din practices General Neurology and Neuropsychiatry in Sarasota, FL. Through affiliation with Lovelace Research Institute, Albuquerque, NM, he functioned as Principal Investigator in over 60 clinical trials, helping bring to market drugs in Epilepsy, Multiple Sclerosis, Neuropathic Pain, and Parkinson's Disease. In May 2008, Dr. Aung-Din founded AfGin Pharma, LLC, a research and development biotech company dedicated to Direct Effects Topical Neuro-Affective Therapy, a novel non-systemic delivery of neuro-active compounds he discovered useful in treating neurological and neuropsychiatric conditions. The therapy is unique in that rapid (within 10-30 mins) therapeutic results are achieved without usual systemic side effects and drug interactions. Dr. Aung-Din has been granted 4 patents relating to the technology in EU and by the USPTO.

- See more at: http://www.drug-dev.com/Main/Back-Issues/THERAPEUTIC-FOCUS-Direct-EffectsTM-Diabetic-Neurop-944.aspx#sthash.Pk2J54OY.dpuf