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Nuchal Apo Therapy for Parkinson's

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Nuchal Topical Neuro-Affective Therapy: A Novel Treatment for Parkinson's Disease Using Apomorphine

By: Ronald Aung-Din, MD

INTRODUCTION

Approved medical therapy for Parkinson's disease (PD) in the US is limited to oral and subcutaneous (sub-Q) injection. The tablet, in ordinary or oral-dissolving form (ODT), is used to deliver levodopa (L-Dopa) to the central nervous system (CNS) in combination with carbidopa (Sinemet and Parcopa) or with a COMT (Catechol-O-Methyl-Transferase) inhibitor (with Comtan as Stalevo). The dopamine (DA) agonists, MAO (Mono-Amine Oxidase) inhibitors, COMT inhibitors, and the anti-cholinergic agents for PD (Artane, Cogentin), are all also in pill form.[1] The DA agonist apomorphine (Apo) is approved as a rescue sub-Q injection (Apokyn) for the acute treatment of episodes of hypomobility/off-periods associated with later stages of PD. Apo injection is also administered by continuous infusion pump.[2]

All current PD treatment modalities are considered systemic in that therapeutic effect relies on drug reaching target sites in CNS through blood flow. Drug first enters the systemic circulation after absorption through the gastrointestinal (GI) tract (with oral preparations) or through subcutaneous vessels (with sub-Q injection or transdermal patch); then, by cardiac output and cerebral blood flow, to intended target areas. The transdermal DA agonist (rotigotine) patch, Neupro, although applied to the skin, requires active drug absorption into sub-Q blood vessels for eventual delivery to the CNS. Neupro was taken off the US market after technical problems with crystallization within the patch matrix. It remains available in Europe with efforts underway to reintroduce it in the US.

With reliance on blood flow for therapeutic effect, idiosyncrasies of the cardiovascular and cerebrovascular systems are important considerations with systemic delivery. Heart disease and cerebral atherosclerosis, common in elderly PD patients, can impact blood flow, influencing drugs reaching the CNS. With oral PD drugs, GI issues affecting GI transit, absorption, and hepatic metabolism present concerns.[3]

SYSTEMIC PD DRUG THERAPY: SIDE EFFECTS & MOTOR COMPLICATIONS

The widespread presence of active drug in systemic and cerebral blood is likely the primary source of side effects associated with PD drugs. As stimulation of DA receptors and other neuro-chemical effects occur at regions other than intended, unwanted drug effects occur. Common side effects include lethargy, nausea, fatigue, orthostatic blood pressure changes, hallucinations, and other behavioral changes. With DA agonists, like pramipexole (Mirapex), obsessive-compulsive behaviors in the form of pathologic gambling and hypersexuality may occur. Episodes of suddenly falling asleep during activities of daily living have also been reported, contributing to auto accidents.[4]

Systemic PD drugs also raise the concern of non-physiologic effects as drug is delivered to downstream neuro-anatomical structures before those upstream. Within the DA system, the sequence of neuro-chemical flow and

TABLE 1

Patient	Sex	Age	Duration PD (Years)	Current PD Medications	UPDRS Motor Pre, Post, Diff
EB	F	86	8	Stalevo (Sinemet & Comtan)	51, 32, 19
GV	M	87	12	Stalevo	38, 18, 20
EK	F	75	6	Sinemet & Mirapex	36, 19, 17
WH	M	88	11	Sinemet & Mirapex	51, 31, 20
SK	F	89	5	Sinemet	66, 52, 14
IR	M	64	10	Sinemet, Mirapex & Amantatine	57, 34, 23

* Expanded UPDRS motor score of 27 items: 0 (nl) to 108 (27x4) range 1.0 mg of apomorphine in Lipoderm except 0.5 mg in patient EK.

Topical Apomorphine Therapy in Off-State Parkinson's Patients: Changes In UPDRS Motor Scores*

effect begins in the brainstem substantia nigra pars compacta, where DA is produced, then to the striatum (caudate and putamen) via ascending nigra-striatal pathways. From the striatum, additional DA effects occur through connections to cortical and sub-cortical motor areas and other structures.[5-7]

The cardinal clinical signs and symptoms of PD (tremor, rigidity, postural instability, and bradykinesia) are thought to occur when DA production in substantia nigra is reduced by 60% to 70% through loss of DA-producing neurons. PD is considered a neuro-chemical disorder resulting primarily from the loss of DA function in the CNS. Recent reports suggest other neuro-transmitters, specifically serotonin (5-HT) and norepinephrine (NE), may also play important roles.[7-9] These other neuro-transmitters may contribute to the non-motor aspects of PD: anxiety, depression, restlessness, sleep disturbance, muscle aches and pains, bowel dysfunction, and loss of smell and appetite with associated weight loss.

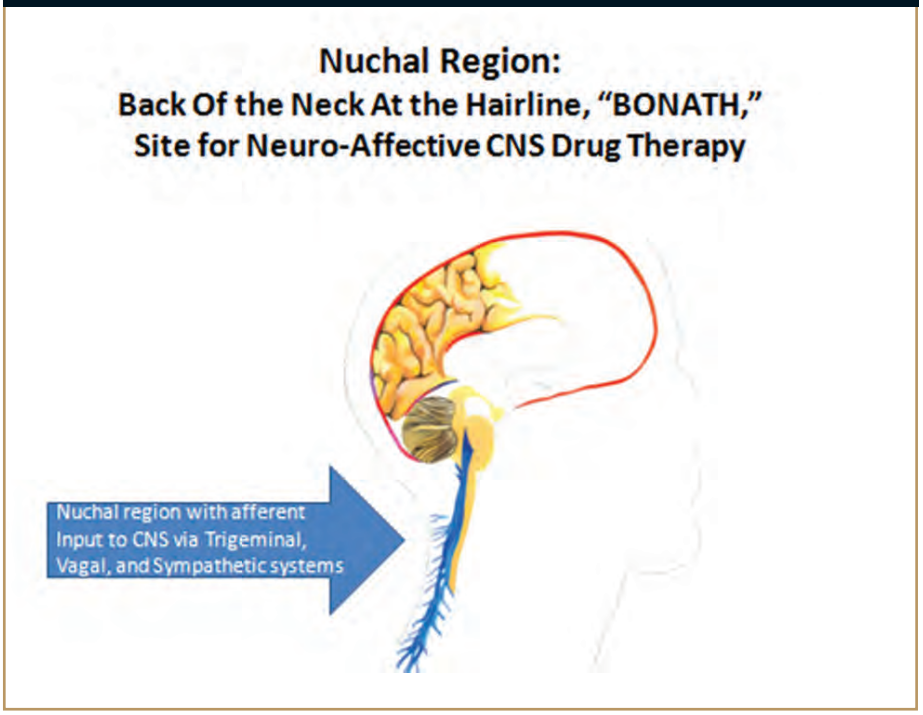
Current PD drug therapy is aimed at providing DA to affected pathways and receptors deficient in the neuro-chemical. This is achieved by boosting the brain's endogenous DA function or by providing exogenous DA as L-Dopa. The function of DA produced in the CNS (endogenous DA) may be enhanced by DA agonists and drugs that reduce DA metabolism and breakdown, allowing a more prolonged DA effect. COMT and MAO-B inhibitors are in this latter category of drugs.[1,2,5,6]

However, there eventually comes time in the clinical course of PD when endogenous DA is incapable of supporting the DA requirements of the patient and alleviating the progression of symptoms. It is at this point exogenous DA is added to the drug regimen. In addition, when clinical symptoms are already significant at the time of diagnosis, exogenous DA is often started early. It is still unclear whether the motor complications of late-stage PD are the result of receptor hypersensitivity from prolonged and fluctuating exogenous DA exposure or part of the natural course of disease, or both. Further, long-term exogenous DA effect at downstream DA receptors (in the striatum and subcortical/cortical structures) could conceivably produce negative feedback inhibition of DA synthesis in the substantia nigra. Whether this potential for suppressing endogenous DA accelerates PD progression needs consideration.[5-8]

The recognized disadvantages of exogenous DA therapy as L-dopa include its short half-life, inducing pulsatile stimulation of DA receptors; its decrease in effectiveness over time; and the emergence of dyskinesias and motor (and non-motor) fluctuations after prolonged use.

It would seem PD drug therapy is best realized when DA effect follows the normal physiologic sequence: brainstem to striatum to subcortex and cortex. This may particularly be true for the DA precursor, L-Dopa, and DA agonists. As discussed, the long-term exogenous DA effects of receptor hypersensitivity (motor complications and on-off phenomena) may result from the persistent, fluctuating, non-physiologic downstream DA receptor stimulation of these drugs.

FIGURE 1

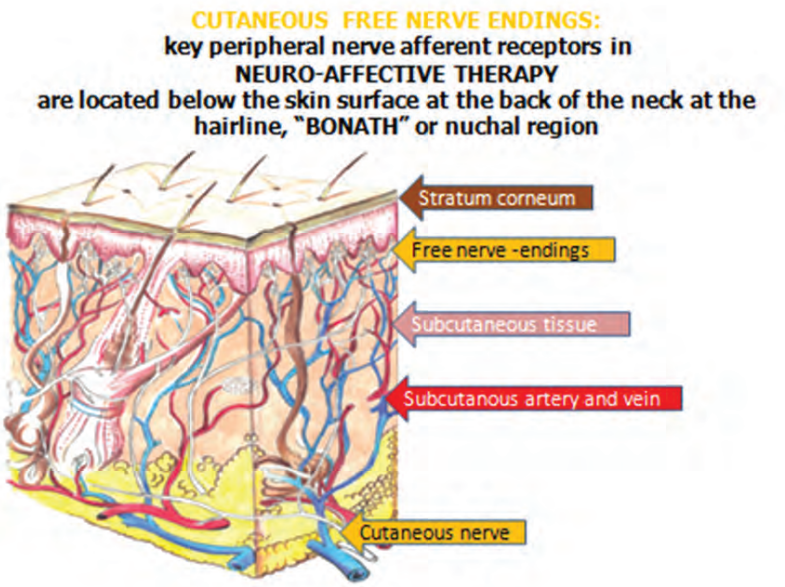


UNIQUE & REVOLUTIONARY NATURE OF NUCHAL TOPICAL APOMORPHINE NEURO-AFFECTIVE THERAPY

Nuchal Apo therapy for PD operates through free nerve endings below the skin surface (stratum corneum) at the upper posterior cervical or nuchal region: back of the neck at the hairline (BONATH). These have direct afferent connections through cervical nerves and nerve roots to afferent components of the Trigeminal Nerve System (the Trigemino-Cervical Complex), the Cervical Sympathetics, and Vagus Nerve that input to the brainstem and the CNS. At no other location is there neural circuitry to this extent between cutaneous free nerve endings and CNS through afferent networks as at the nuchal region or BONATH (Figures 1, 2, and 3).[3]

Afferent impulses are those from the body (skin, muscle, and internal organs) to CNS, and efferent impulses originate in the CNS and flow out to the body. Exposed, un-myelinated free nerve-endings at the nuchal region function as peripheral nerve afferent receptors. When affected by certain topically applied CNS-active drugs, they influence

FIGURE 2



CNS efferent outflow to modulate/reduce clinical symptoms. The cutaneous free nerve endings are easily accessible to drugs compounded in an appropriate dermal penetration-enhancing medium and applied to the skin.

In the instance of nuchal Apo, the compounded Apo cream (1.0 mg/0.5 ml Lipoderm) is gently rubbed into the skin at BONATH over an approximate 15- to 20-sq-cm area at both sides of midline. Roughly estimated, there are in the order of hundreds of thousands to millions of free nerve endings in this area of topical drug application providing afferent feedback to CNS through extensive neural connections.

REGARDING OTHER POSSIBLE MECHANISMS

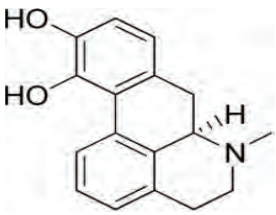
The possibility that nuchal Apo clinical effect is through topical drug entering sub-Q vessels and working through the vascular system is unlikely in consideration of the observed times of therapeutic effect, generally 5 to 10 minutes. The time to therapeutic benefit is too short to account for drug diffusion across concentration gradients in the subcutaneous tissue and absorption into the vascular system. Cardiac output and cerebral blood flow factors also need to be considered. Therapeutic blood levels must be achieved for clinical effect in systemic drug delivery. Doses of Apo used in nuchal therapy (1 to 2 mg applied topically) would be insufficient to provide therapeutic drug concentrations in consideration of dilution in systemic and cerebral blood.

Systemic delivery by transdermal patch is analogous to filling a reservoir to achieve a therapeutic drug level in blood. In contrast, topical neuro-affective therapy at the nuchal region may be viewed as the discharge of an electrical capacitor that results in neural impulse formation and propagation - following cutaneous free nerve ending effect by active drug. In this respect, the significant disparity in time to clinical effect comparing nuchal topical therapy to systemic drug delivery by transdermal patch or oral means makes sense.

The possibility that nuchal Apo effect is on the basis of up-take of drug via a neuronal process (of free nerve endings) with retrograde axonal transport to CNS is likewise unlikely. Again, the relatively short times to clinical effect and the low drug concentrations used in nuchal Apo are against this mechanism.

An additional question is whether application of compounded topical Apo cream at sites other than the nuchal region or BONATH, for instance, the arm or leg, would work in treating PD. I believe the answer to be no, not very likely. The distance from the cutaneous free nerve endings and peripheral nerves at these locations to the spinal cord and CNS is relatively much greater. Further, the extensive afferent neural network with Trigeminal, Sympathetic, and Vagal systems, essential to the CNS effects of nuchal therapy, does not exist at these other areas.[3]

TABLE 2



Formula	$C_{17}H_{17}NO_2$
Mol. mass	267.322 g/mol

Apomorphine (Apokyn, Ixense, Spontane, Uprima) is a non-selective dopamine agonist which activates D1-like and D2-like receptors. It is a morphine decomposition product, hence the -morphine suffix. Apomorphine does not contain morphine or bind to opioid receptors. It is a potent emetic (ie, it induces vomiting) and should not be administered without an antiemetic. It is used to induce therapeutic emesis in veterinary medicine. Pharmacology: Apomorphine affinity for receptors:

Dopamine	Serotonin	Norepinephrine
D_1 (K_i = 372 nM)	5-HT_{1A} (K_i = 117 nM)	α_{1B}-adrenergic (K_i = 676 nM)
D_{2S} (K_i = 35 nM)	5-HT_{2A} (K_i = 120 nM)	α_{1D}-adrenergic (K_i = 65 nM)
D_{2L} (K_i = 83 nM)	5-HT_{2B} (K_i = 132 nM)	α_{2A}-adrenergic (K_i = 141 nM)
D_3 (K_i = 26 nM)	5-HT_{2C} (K_i = 102 nM)	α_{2B}-adrenergic (K_i = 66 nM)
D_4 (K_i = 4.4 nM)		α_{2C}-adrenergic (K_i = 36 nM)
D_5 (K_i = 15 nM)		

Apomorphine Data

THE ADVANTAGE OF NUCHAL APO THERAPY

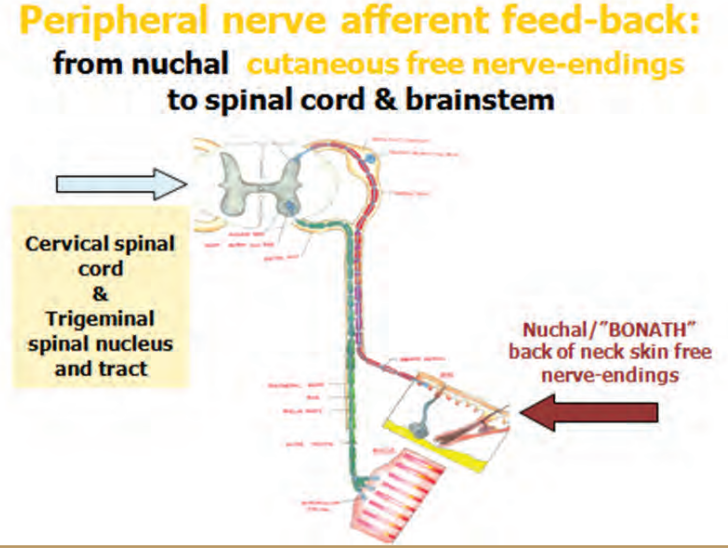
The therapeutic benefit of nuchal Apo in PD is achieved by its effect on cutaneous free nerve endings at the back of the neck. Commercially available Apo powder is formulated in a proprietary manner in a compounding medium (Lipoderm) to allow dermal penetration of active drug to the nerve endings.

In operating through neural mechanisms rather than blood flow, systemic and cerebral side effects are minimized or avoided. Therapeutic effect is also more rapid than with pill or transdermal patch, as concentration gradients within subcutaneous tissues for drug absorption into blood vessels are unnecessary. While sub-Q Apo injection (Apokyn) is fairly rapid in onset (15 to 30 minutes), there exists the potential for a bolus effect with exaggerated side effects and wash-out of therapeutic drug effect. Further, to counter the very possible side effects of nausea and vomiting with Apokyn, a 3-day pre-treatment regimen with the anti-emetic trimethobenzamide (Tigan) is recommended. An initial dose determination process under the supervision of a healthcare provider is also required. Finally, this form of PD drug therapy is considered invasive and unacceptable to individuals who are needle phobic.[2]

As discussed, therapeutic drug effect with nuchal Apo therapy follows physiologic lines as it begins at the cutaneous free nerve endings; continues by peripheral nerves to cervical nerve roots and spinal cord; then, from brainstem structures (substantia nigra), via ascending nigra-striatal pathways, to striatum and other downstream structures. With systemic delivery, active drug is haphazardly delivered to neural structures by blood flow, contrary to physiologic neuro-anatomical sequence. As such, active drug affects areas not specifically targeted, causing unwanted side effects, such as the significant nausea encountered with Apo sub-Q injection.

FIGURE 3

RELATION OF CERVICAL FREE NERVE ENDINGS, PERIPHERAL NERVES, AND NERVE ROOTS TO CERVICAL CORD



CLINICAL EXPERIENCE WITH NUCHAL APO IN PD

To date, my associate, Bridget Keller, MD, and I have treated more than 60 PD patients with nuchal Apo through our neurology practice in Sarasota, Florida. Our observations indicate nuchal Apo alleviates clinical symptoms of PD in a measurable way more than 85% of the time when patients are treated in a relative off-state, exhibiting symptoms of tremor, rigidity, postural instability, and reduced spontaneity. Symptom improvement after topical application of 1 mg/0.5 ml compounded Apo to the back of the neck was generally clinically obvious within 15 minutes. Except for a few patients who developed slight localized skin irritation, no significant side effects have been noted. In these individuals, changes in the compounding formula were made. Clinical benefit on average lasted 4 hours, with some patients reporting longer.

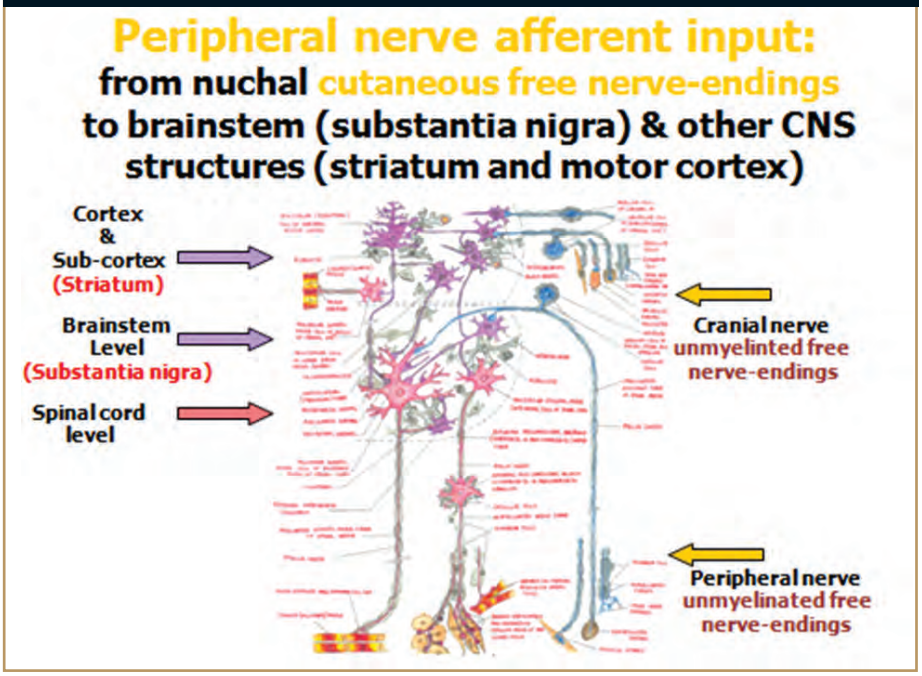
Of the aforementioned patients, two have passed the 1-year mark for continuous twice-daily use of nuchal Apo for PD. There have been no significant side effects with chronic use or the need to increase dose to maintain therapeutic benefit. On the contrary, after a period of several weeks to

TABLE 3

Potential Benefits of Nuchal Apo In PD

- Quick onset of action, 10-15 minutes, with duration of effect up to 3-4 hours.
- Demonstrates efficacy in reducing tremor and rigidity; improves psychological affect/sense of well-being in patients in the off-state at different stages of PD, from mild to severe.
- Use of nuchal Apo can reduce use of other PD medications, simplifying therapy and eliminating side effects associated with concomitant medications, of particular importance in the elderly.
- Nuchal Apo is easily administered and without significant side-effects.
- May preserve DA neuronal function, minimize motor complications, and delay disease progression and need for exogenous DA in PD by facilitating endogenous DA: neuro-protective.
- Allows use of a clinically proven drug for PD (apomorphine) in a novel and more convenient manner.
- Bypasses the Blood-Brain-Barrier.

FIGURE 4



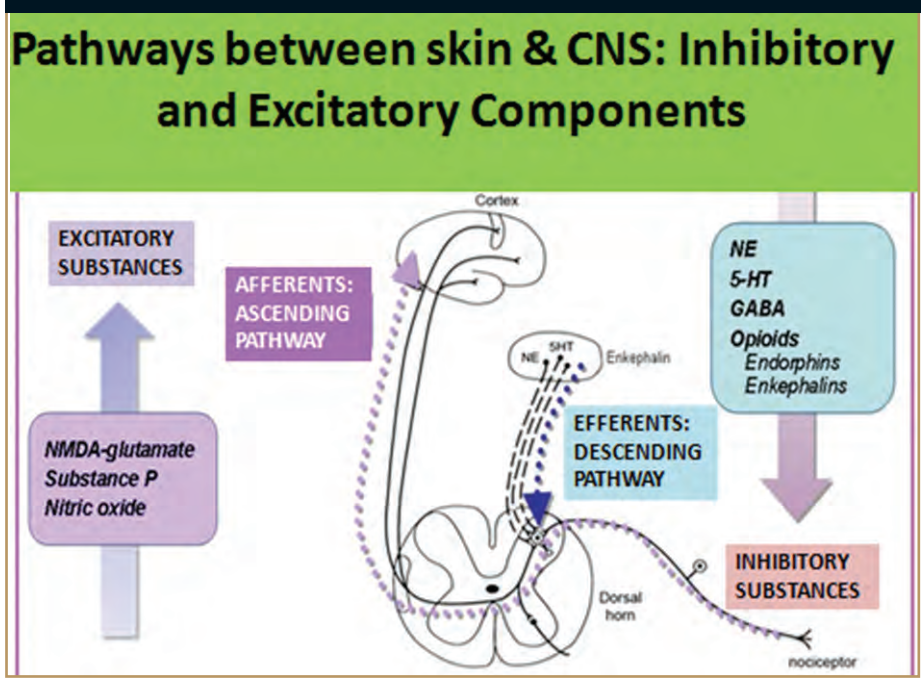
months, some patients were able to reduce their dose of nuchal Apo and concomitant PD drugs.

Table 1 outlines the results of nuchal Apo in six established PD patients. These results exemplify those observed in other treated patients. The expanded Unified Parkinson's Disease Rating Scale (UPDRS) was used to objectively assess the functional states of patients pre- and post-treatment. Twenty-seven (27) components of the clinical neurological exam are rated on a 0 to 4 scale in regard to severity: 0 = normal and 4 = severe, thus giving a range of 0 to 108.6

As can be appreciated by the UPDRS scores, these six patients were significantly affected by PD. The average pre-treatment score in their relative off-state was 50. Within 15 to 30 minutes of topical application of compounded Apo (0.5 to 1.0 mg), all six patients were improved, as reflected by reductions in their UPDRS scores. The average UPDRS score post-treatment was 31, indicating an average improvement for the group of 19 points.

The duration of clinical motor function improvement in these patients was reported at 2.5 to 26 hours (with average of 4 hours), representing the period patients felt they were able to function off their usual PD medications. This was attributed to the therapeutic benefit of nuchal Apo. After treatment with nuchal Apo, patients returned to their previous PD drug regimen, consisting of taking medications 3 to 4 times per day. By their own accounts, and of their caretakers, their current PD therapy was considered sub-optimal. The only side effects expressed were transient fatigue and dizziness, in patients EK and SK. The relationship of these symptoms to nuchal Apo was unclear. As additional documentation, patients were videotaped pre- and post-nuchal Apo treatment.

FIGURE 5



NON-MOTOR EFFECTS OF NUCHAL APO & YET TO BE DETERMINED MECHANISMS

In addition to the significant improvement in motor function as reflected by the post-treatment reduction in UPDRS scores, patients also expressed an improved sense of well-being after nuchal Apo. Some noted an overall decrease in perceived muscle tone that was accompanied by a relaxed feeling.

Anxiety and psychological tension are common non-motor manifestations of PD. These may pre-date motor symptoms by several years. The observed improvement in non-motor function may be attributed to the alpha-adrenergic and serotonergic effects of Apo when administered as nuchal Apo. Apo is thought to function primarily as a DA agonist in the clinical setting. However, it has recognized effects on norepinephrine and serotonin receptors, some quite significant in vitro. It is possible the potential non-motor

effects of Apo in PD are generally masked by the more significant and overriding symptoms of nausea and other systemic effects seen with traditional Apo therapy as sub-Q injection, Apokyn (Vernalis/Ipsen).[15-17]

Recall therapy with sub-Q Apo for PD requires a 3-day pre-treatment regimen with an oral anti-emetic; this may need to be continued throughout therapy. The potent emetic (nausea inducing) property of Apo is used to advantage in treating ingestion of poisons and other toxic substances in man and animals in which therapeutic emesis is required. These side-effects, on the other hand, have not been noted with nuchal Apo as there is presumed negligible to no systemic Apo effect (Table 2).[15]

Dopmine, norepinephrine, and serotonin pathways from brainstem to frontal cortex and limbic structures influence mood and pleasure as well as alertness and focus. These likely play a role in the non-motor symptoms of PD and other neuro-chemical disorders of the brain (Figures 4, 5, and 6).[7]

The exact mechanisms by which a topically applied agonist drug, like Apo, affects cutaneous free nerve endings at the nuchal region to modulate inhibitory and excitatory influences on the ascending and descending neural pathways to produce clinical effect has yet to be fully determined. Additional studies with other agonist and antagonist agents may help shed light on this phenomenon (Figures 5 and 7).

CONCLUSIONS & FUTURE IMPLICATIONS

These preliminary open-label findings in an outpatient office setting suggest potential utility for nuchal Apo therapy in the management of PD. This form of Apo has also been used in other movement disorders, such as benign essential tremor and tremor associated with multiple sclerosis (MS), stroke, and cerebellar degeneration, with similar efficacy. Plans are underway for a formal double-blind, placebo-controlled, parallel-group crossover study to confirm these preliminary results and establish proof-of-concept.

There is strong neuro-physiological logic to suggest nuchal Apo may help preserve DA function in the striatum, minimizing motor complications and delaying disease progression in PD. This may occur as nuchal Apo augments endogenous DA function by utilizing established neural pathways, as opposed to haphazard, non-physiologic stimulation of DA receptors that occurs with drug delivery through blood flow. Accordingly, nuchal Apo would act to enhance endogenous DA production and utilization. The potential for negative feedback inhibition of DA production in substantia nigra, as may occur with prolonged exogenous DA therapy, is likewise avoided.

FIGURE 6

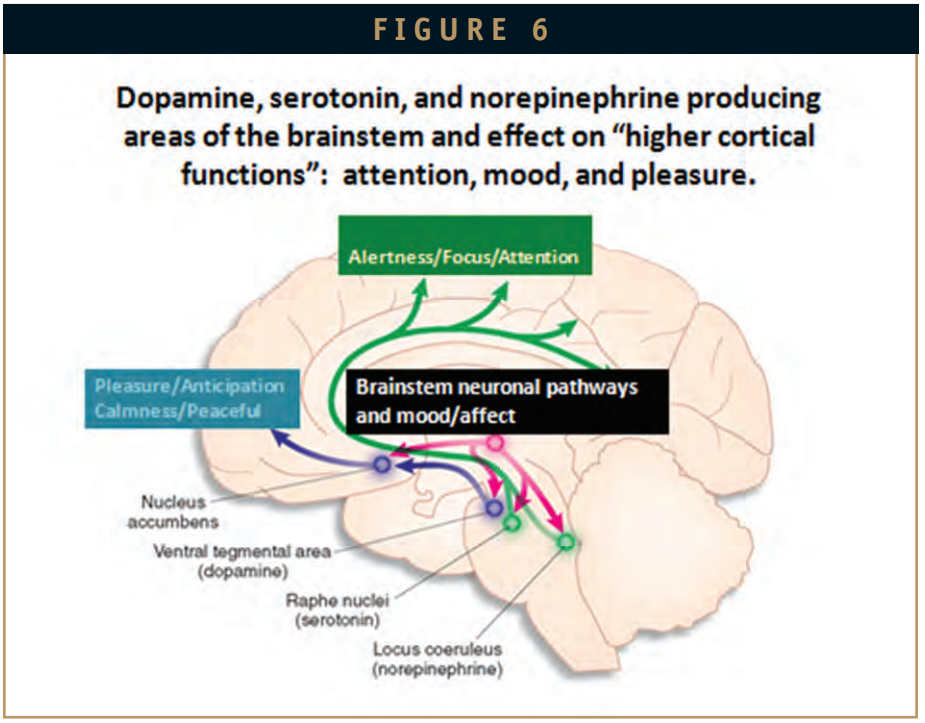
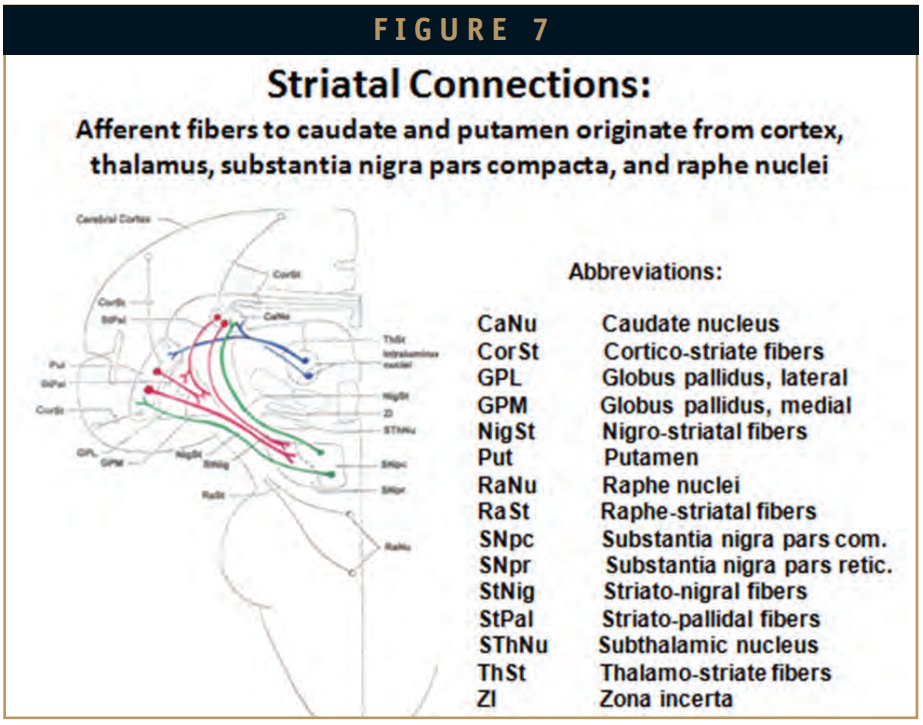


FIGURE 7



ACKNOWLEDGEMENTS

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BIOGRAPHY

Dr. Ronald Aung-Din is certified by the American Board of Psychiatry and Neurology and is a member of the American Academy of Neurology. He practices General Neurology and Neuropsychiatry in Sarasota, FL. After studies in Mechanical and Environmental Engineering at Bucknell (Lewisburg, PA) and Cornell (Ithaca, NY) Universities, he worked in industry as a supervising engineer. He then attended Columbia University in New York City for Pre-Medical studies, followed by Medical School at the University of Texas Southwestern Medical School, Dallas, TX. Residencies in Neurology and Neurosurgery were at the University of Florida, Gainesville, FL. Additional studies included a Medical Student Fellowship in Cardiology at the Radcliffe Infirmary, Oxford and a Clinical Neurology Post-Graduate Fellowship at the National Hospital for Nervous Disease, Queen Square, London, UK.