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Loder et al.

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- (54) **TREATMENT OF FATIGUE, HEAD INJURY AND STROKE**
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- (58) **Field of Search** 514/561, 217, 514/239.2, 649, 438, 613

- (56) **References Cited**
U.S. PATENT DOCUMENTS
4,431,670 A * 2/1984 Heller
6,096,737 A * 8/2000 Loder
FOREIGN PATENT DOCUMENTS
GB 2 297 868 8/1996
GB 2 309 774 8/1997

- OTHER PUBLICATIONS**
Merck Manual 15th edition, p. 1381, 1987.*
Gulick, E.E., "Model Conformation of the MS-Related Symptom Checklist", *Nursing Research*, 1989; 38:147-153.
Fisk, J.D. et al., "The Impact of Fatigue on Patients with Multiple Sclerosis", *The Canadian Journal of Neurological Sciences*, 1994; 21:9-14.
Moore, R.Y. and Bloom, F.E., "Central Catecholamine Neuron Systems: Anatomy and Physiology of the Norepinephrine and Epinephrine Systems" *Annual Review of Neuroscience* 1979; 2:113-168.
Smith, B.H. and Sweet, W.H. "Neuroscience for the neurosurgeon; Monoaminergic Regulation of Central Nervous System Function: I. Noradrenergic Systems", *Neurosurgery*, 1978; vol. 3, No. 1:109-119.
Ingles, J.L. et al. "Fatigue After Stroke", *Archives of Physical Medicine and Rehabilitation*, Feb. 1999; vol. 80, No. 2:173-177.
Boyeson, M.G. et al. "Sparing of Motor Function After Cortical Injury", *Archives of Neurology*, Apr. 1994:51:405-413.
Feeney, D.M. et al. "Noradrenergic Pharmacotherapy, Intracerebral Infusion and Adrenal Transplantation Promote Functional Recovery After Cortical Damage", *Journal of Neural Transplantation and Plasticity*, Jan.-Mar. 1993; vol. 4, No. 3:199-213.

- Weiss, J.M. et al., "Behavioral Depression Produced By An Uncontrollable Stressor: Relationship to Norepinephrine, Dopamine, and Serotonin Levels in Various Regions of Rat Brain", *Brain Research Reviews*, Oct. 1981, vol. 3, No. 2:167-205.
- Clauw, D.J. M.D. "Fibromyalgia: More Than Just a Musculoskeletal Disease" *American Family Physician*, Sep. 1, 1995; vol. 52, No. 3:843-851.
- Glynn, C.J. et al.; "Role of Spinal Noradrenergic System In Transmission of Pain in Patients With Spinal Cord Injury", *The Lancet*, Nov. 29, 1986; vol. II, No. 8518:1249-51.
- Reddy, S.V.R. et al., "Spinal Cord Pharmacology of Adrenergic Agonist-Mediated Antinociception", *The Journal of Pharmacology*, Jun., 1980; vol. 213, No. 3:525-533.
- Feeney, et al.; "From Laboratory to Clinic: Noradrenergic Enhancement of Physical Therapy for Stroke or Trauma Patients", *Advances in Neurology*, 1997; vol. 73:383-394.
- Boyeson, M.G. "Intraventricular Norepinephrine Facilitates Motor Recovery Following Sensorimotor Cortex Injury", *Pharmacology Biochemistry and Behavior*, Mar. 1990; vol. 35, No. 3:497-501.
- Boyeson, M.G. and Harmon, R., "Effects of Trazodone and Desipramine On Motor Recovery In Brain-Injured Rats", *American Journal of Physical Medicine and Rehabilitation*, Oct. 1993; vol. 72, No. 5:286-293.
- R.J. Valentino et al. "Antidepressant Actions on Brain Noradrenergic Neurons", *The Journal of Pharmacology and Experimental Therapeutics*, May 1990; vol. 258, No. 2:833-840.
- Boyeson, M.G. et al., "Comparative Effects of Fluoxetine, Amitriptyline and Serotonin on Functional Motor Recovery After Sensorimotor Cortex Injury", *American Journal of Physical Medicine & Rehabilitation*, Apr. 1994; vol. 73, No. 2:76-83.

(List continued on next page.)

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(57) **ABSTRACT**

A method of treatment of disorders of neurological origin and drug formulations for use in the method are disclosed. These conditions comprise fatigue and associated syndromes of pain, weakness and depressed mood which are associated with chronic fatigue syndrome, brain injury and stroke, stress, fibromyalgia, and irritable bowel syndrome. The treatment comprises administering to a patient in need thereof a selective inhibitor of noradrenaline reuptake combined with either phenylalanine or tyrosine in the same dosage form or the same pack.#

The noradrenergic drug may be selected from lofepramine, desipramine or reboxetine. The selective inhibitor may be a combined inhibitor of both noradrenaline and serotonin reuptake such as venlafaxine, duloxetine or milnacipran, or an inhibitor of both noradrenaline and dopamine reuptake such as bupropion.