

A drug combination that reduces weight gain associated with antidepressant therapy

Newer generation antidepressants seem less likely to be associated with cardiovascular side effects and toxicity associated with older generation antidepressants, such as tricyclic antidepressants or monoamine oxidase inhibitors (MAOIs). Currently, newer generation antidepressants include selective serotonin reuptake inhibitors (e.g., fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram), venlafaxine, duloxetine, nefazodone, mianserin, setiptiline, viquiline, trazodone, cianopramine, and mirtazapine. Weight gain has been a major concern with certain of the newer antidepressants, particularly, with paroxetine (PAXIL® PAXIL CR®) and mirtazapine (Fava, J. Clin. Psych. 61 (suppl. 11):37-41 (2000); Carpenter et al, J. Clin. Psych. 60:45-49 (1999); Aronne et al, J. Clin. Psych. 64 (suppl. 8):22-29 (2003), both of which are incorporated by reference herein in their entirety). A large proportion of patients treated with paroxetine, mirtazapine, and other antidepressants, such as venlafaxine (EFFEXOR®, EFFEXOR XR®), gain a significant amount of weight. Most of these patients find it difficult to lose the weight gained as a result of treatment, even after discontinuing use of the particular antidepressant. Weight gain is unacceptable in patients and a major reason for noncompliance with antidepressant therapy (Cash et al, Percep. Motor Skills 90:453-456 (2000); Deshmukh et al, Cleveland Clinic J. Med. 70:614-618 (2003). It is believed that potential mechanisms for the observed weight gain include histamine H1 receptor antagonism for mirtazapine, and anticholinergic effects in the case of paroxetine.

Zonisamide is a marketed anticonvulsant indicated as adjunctive therapy for adults with partial onset seizures. It is believed that the mechanism of antiepileptic activity appears to be: 1) sodium-channel blocking; and, 2) reduction of inward T-type calcium currents. In addition, zonisamide binds to the GABA/benzodiazepine receptor complex without producing change in chloride flux. Further, zonisamide facilitates serotonergic and dopaminergic neurotransmission and possesses a weak inhibitory effect on carbonic anhydrase.

Zonisamide has been shown to cause significant weight loss (comparable to marketed weight loss medications) in patients presenting with primary obesity (Gadde et al, JAMA 289:1820-1825 (2003). It has been postulated that it is the effect of zonisamide on the CNS concentration of serotonin, dopamine and carbonic anhydrase that is responsible for this effect. There is evidence that zonisamide increases serotonin and dopamine synthesis rates (Hashiguti et al, J Neural Transm Gen Sect.

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1993;93:213-223; Okada et al, Epilepsy Res. 1992;13:113-119, both of which are incorporated by reference herein in their entirety). There is further evidence suggesting that zonisamide stimulates dopamine D₂ receptors (Okada et al, Epilepsy Res. 1995;22:193-205, incorporated by reference herein in its entirety). Zonisamide was well tolerated, fatigue being the only side effect that occurred more frequently than with placebo treatment.

Thus, the present inventors have determined that the use of anticonvulsants in general is effective in reducing or preventing the weight gain associated with the use of medications such as antidepressants, particularly newer generation of antidepressants, antihistamines, and serotonin receptor antagonists, such as 5HT_{2c} receptor antagonists.

Aspects of the present invention provide, at least in part, methods of reducing the risk of weight gain associated with antidepressant therapy. These methods involve the use of weight-loss promoting anticonvulsants. The methods of the present invention are also effective against individuals who have gained weight irrespective of the use of antidepressants.

Patents

Patent Number: 7,429,580

Title: COMPOSITIONS OF AN ANTICONVULSANT AND AN ANTIPSYCHOTIC DRUG AND METHODS OF USING THE SAME FOR AFFECTING WEIGHT LOSS

Country: United States of America

Patent Number: 7,713,959

Title: A method for reduction of weight gain associated with antidepressant therapy

Country: United States of America

Patent Number: 2005206139

Title: A method for reduction of weight gain associated with antidepressant therapy

Country: Australia