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Bodyweight Gain and Anticonvulsants
A Comparative Review

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Contents

Abstract

Bodyweight gain is a common and frequent undesirable effect associated with the use of anticonvulsant drugs. This has been observed for many years with valproic acid (sodium valproate) and carbamazepine, and also, more recently, with some of the newer anticonvulsants such as vigabatrin and gabapentin.

Very often bodyweight gain in children, adolescents and adults with epilepsy taking such anticonvulsants results in cosmetic adverse effects. On the other hand, bodyweight gain is disturbing to general health, with a possible increase in the risk of diabetes mellitus or heart disease. Other potential adverse effects, such as the association of obesity with polycystic ovaries, have been reported with the use of valproic acid.

Potential mechanisms of anticonvulsant-associated bodyweight gain are not yet clear and differ between drugs used. The involvement of lowered blood glucose level, which may stimulate eating through an effect on the hypothalamus, constitutes one of the possible mechanisms. Lowered blood glucose levels may result from a competition between the binding of the drug and long chain fatty acids. An increased availability of the latter stimulates insulin production and lowers the serum glucose levels. Another possible explanation for lowered blood glucose may be a deficiency in carnitine directly caused by the drug, that would result in a reduction of fatty acid metabolism and an increase in glucose consumption. An enhancing effect of γ-aminobutyric acid-mediated neurotransmission may increase appetite for carbohydrates and reduce energy expenditure. An antidiuretic hormone-like effect or effects on norepinephrine (noradrenaline) or serotonin-mediated neurotransmission are more rarely considered. Many studies on

anticonvulsant-associated bodyweight gain illustrate how we could better define the risk factors for the development of anticonvulsant-induced bodyweight gain and uncover the mechanisms behind it.

Marked bodyweight gain can be caused by drugs belonging to many pharmacological groups and is a common problem with the use of anticonvulsants. This has been observed over many years with valproic acid (sodium valproate) and carbamazepine and also, more recently, with some of the newer anticonvulsants. The studies investigating this association emphasise the importance of age, gender, drug dose, pre-existing conditions and inherent susceptibility to bodyweight modifications associated with anticonvulsants.

Potential mechanisms of anticonvulsant-associated bodyweight gain are not yet elucidated and depend on the drug used. Different ways in which anticonvulsants could affect regulation of bodyweight are analysed in this review.

This undesirable adverse effect is often observed in young patients and disturbs general health, causing cosmetic adverse effects. It can jeopardise compliance with epilepsy treatment. With some anticonvulsants, bodyweight gain can increase long-term risk for health problems, including continued obesity in adulthood, hypertension and, in women, a potential risk of polycystic ovaries and hyperandrogenism.

The following sections review the mechanisms of the regulation of bodyweight as well as the major anticonvulsants implicated in bodyweight gain and the clinical implications of this adverse effect.

1. How to Measure Bodyweight Gain

One of the most important difficulties when evaluating bodyweight gain is determining whether a patient has really gained bodyweight, because the practitioner often has not weighed the patient before initiating treatment.

Nevertheless, in a large number of studies, bodyweight gain is usually evaluated by comparing bodyweight after a particular period of treatment with the bodyweight at the initiation of treatment. Excessive bodyweight gain has to be confirmed by different anthropometric parameters. These measurements are important to detect changes before severe adverse effects are experienced.

Measurement of total body fat content is the most precise way to evaluate obesity, but this measurement is too difficult and too costly to be used on a routine basis.

Regular measurements of bodyweight and height and the calculation of body mass index (BMI) provide a quantitative way to monitor an adverse effect that has great impact on quality of life in patients with epilepsy. BMI is calculated from the bodyweight in kilograms divided by the square of standing height (or supine length in small children) in metres and is reported in units of kg/m^2. Obesity, in persons aged >19 years, is defined as BMI ≥27.8 for men and ≥27.3 for women. In adolescent boys, obesity is defined as BMI ≥23 for age 12 to 14 years, ≥24.3 for age 15 to 17 years and ≥25.8 for age 18 to 19 years. In adolescent girls, the BMI defining obesity is ≥23.4 for ages 12 to 14 years, ≥24.8 for ages 15 to 17 years and ≥25.7 for ages 18 to 19 years. The 85th percentile is used as the upper limit for normal bodyweight. In one study,[1] patients were classified as non-bodyweight gainers if the bodyweight gain was <5% over baseline bodyweight, mild-moderate bodyweight gainers at 5 to 10% over baseline bodyweight and marked weight gainers at >10% over baseline bodyweight.

In another study[2] concerning only children, bodyweight velocity was calculated as the change in bodyweight over or extrapolated to 1 year. Bodyweight velocity was classified as excessive if it exceeded the 97th percentile expected for a child of that age and gender.

The time to maximum bodyweight gain may be influenced by appointment intervals. Patients with less severe seizure disorders may have their bodyweight measured less frequently.

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2. Anticonvulsants Associated with Bodyweight Gain

2.1 Valproic Acid (Sodium Valproate)

Valproic acid is the drug of choice for a wide variety of epileptic seizures and epileptic syndromes, because of its broad spectrum of activity and the fact that it is most often well tolerated. However, some unwanted adverse effects, including bodyweight gain, have been reported since the first clinical studies with this agent.[3-6] In a summary of the most common adverse effects based on 16 clinical trials involving a total of 1140 patients, bodyweight gain was reported in 3%.[7] However, the reported incidence in consecutive studies varied from 4 to 71% of the different patient populations (table I).

Few studies have focused on this clinical problem. Egger and Brett[9] reported bodyweight gain in 44% of 100 children with epilepsy treated with valproic acid at a daily dosage of 30 to 50 mg/kg. The yearly bodyweight velocity exceeded or reached the 98th percentile in 38 children during the year after the drug was started. The authors stated that 'a direct effect of the drug or a metabolite on the hypothalamus is more likely since small doses of VPA [valproic acid] did not affect bodyweight, whereas doses higher than 30 mg/kg did'. There was no relationship with the type of epilepsy or the degree to which seizures were controlled by the drug.

Table I. Bodyweight gain and valproic acid (sodium valproate) therapy in patients with epilepsy

Study	No. of pts	Patient population	Epileptic syndromes	Percentage of pts with bodyweight gain	Comments
Völzke & Doose[3]	116	Children and adults	Generalised and partial	4	
Hassan et al.[4]	90	Adults	Generalised and partial	7	Increase of appetite
Laljee & Parsonage[8]	320	Adults	Generalised and partial	7.5	
Egger & Brett[9]	100	Children	Generalised and partial	44	Dose related
Feuerstein et al.[6]	149	Children and adults	Generalised idiopathic	8.7	Female predominance (77%)
Covanis et al.[5]	284	Children and adults	Generalised and partial	17	More common in females
Dinesen et al.[10]	63	Adults	Unknown	57	Bodyweight gain >4kg
Bourgeois et al.[11]	118	Children and adults	Generalised idiopathic	11	
Mattson et al.[12]	480	Adults	GTCS and CPS	20	Bodyweight gain >5.5kg
Richens et al.[13]	300	Adults	GTCS, partial	12.1	
Isojärvi et al.[14]	22	Adult females	All types	59	Bodyweight gain range 8 to 49kg
Corman et al.[1]	70	Adults	Not specified	71	24% 5 to 10% bodyweight gain; 47% >10% weight gain
Easter et al.[2]	103	Children	Generalised and partial	9.2	10.7% were obese at study entry
Novak et al.[15]	55	Children	Idiopathic and symptomatic epilepsies	36.4	Correlated with initial bodyweight
Verrotti et al.[16]	40	Adult females	Generalised and partial	37.5	Body mass index >25; higher serum leptin and insulin levels
Bauer et al.[17]	93	Adult females	Partial epilepsies	22.5	No correlation with polycystic ovary syndrome

CPS = complex partial seizures; **GTCS** = generalised tonic-clonic seizures.

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Novak et al.[15] observed changes in BMI in 20 of 55 children, but BMI was already greater than the 90th percentile for age in 14 of the patients at the start of treatment. Bodyweight changes were significantly correlated with initial bodyweight and initial BMI, but not with age at the start of therapy, duration of follow-up, gender, seizure type, aetiology, dose of valproic acid or monotherapy.

Dinesen et al.[10] reported that in 63 adult patients with epilepsy treated with valproic acid, 57% had bodyweight gain of >4kg. The bodyweight gain was not dose related and there were no differences between patients with and without bodyweight gain with regard to age, gender, pretreatment obesity, duration of treatment, dosage of the drug and serum concentrations of valproic acid. The only (but not significant) difference between the two groups of patients was in relation to increase in appetite, thirst and familial predisposition to obesity. No patient showed clinical signs of water retention.

Corman et al.[1] found that 70% of patients gained bodyweight in a population of 70 adult patients with epilepsy receiving valproic acid monotherapy or polytherapy attending an epilepsy clinic. There were no statistically significant differences between males and females regarding the initial starting dose of valproic acid or valproic acid dose at maximum bodyweight gain, nor with regard to gender, age, initial maintenance dose (>1000 *vs* 1000 mg/day), monotherapy versus polytherapy and family history of bodyweight problems.

An increase in alertness and a general feeling of well-being is common and is often associated with an increase of appetite and a consequent increase of bodyweight. Corman et al.[1] and Dinesen et al.[10] reported, that 49 and 46%, respectively, of their patients experienced increased appetite during valproic acid therapy. They also noted increased thirst or increased intake of energy–rich beverages.

Dam and Gram[18] showed a clear relationship between the dose of valproic acid and bodyweight gain. Conversely, Corman et al.[1] and Dinesen et al.[10] did not note this relationship.

2.2 Carbamazepine

Carbamazepine is a widely used anticonvulsant and is considered as the drug of choice for partial seizures and partial epilepsies. Oedema, hyponatraemia, serum hypo-osmolality and bodyweight gain – caused by water retention – have been reported as adverse effects of this agent.[19,20] However, carbamazepine may induce bodyweight gain by fat deposition.

Bodyweight gain during carbamazepine therapy has been reported in very few studies: 2% in a study of 300 patients;[13] 9% in a study of 480 patients;[12] and 14% in a study of 300 patients.[1] Isojärvi et al.[21] reported obesity in 25% of patients taking carbamazepine.

Lampl et al.[22] reported four young patients who developed an increase in appetite, excessive food intake and marked bodyweight gain induced by carbamazepine. Dietary restriction had no effect, but in three of the four patients, all symptoms disappeared within a few months when carbamazepine was discontinued and changed to valproic acid. Conversely, three of eight patients reporting bodyweight gain with valproic acid were switched, because of poor seizure control and adverse effects (including bodyweight gain), to carbamazepine and continued to gain bodyweight.[2]

In a more recent study, Hogan et al.[23] compared the total percentage bodyweight changes during add-on therapy with tiagabine. A total of 349 patients entered the study taking carbamazepine (206 patients) or phenytoin (143 patients). Patients were randomised to adjunctive tiagabine or phenytoin if on carbamazepine or to adjunctive tiagabine or carbamazepine if receiving phenytoin at baseline. Adjunctive tiagabine therapy had no significant effect on total bodyweight, whereas adjunctive carbamazepine therapy was associated with a mean bodyweight increase of 1.5%.

2.3 Vigabatrin

Vigabatrin is an anticonvulsant medication designed to increase the level of γ-aminobutyric acid (GABA) in the brain. Many studies have shown its

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efficacy, particularly in patients with partial seizures and in some childhood epileptic syndromes, especially infantile spasms. However, its use has been recently limited because of reports of visual field constriction.[24]

Bodyweight gain with treatment has been a consistent finding in most preliminary clinical trials of vigabatrin.[25,26] In the European monotherapy study[27] comparing vigabatrin and carbamazepine, vigabatrin was better tolerated than carbamazepine but more frequently associated with bodyweight gain (11 *vs* 5% of patients, respectively). More recently, in the Canadian Vigabatrin Study, a long-term open, add-on trial,[28] a mean bodyweight gain of 3.7 ± 0.2kg was observed by the end of the study.

2.4 Gabapentin

Gabapentin is a well tolerated anticonvulsant, structurally related to GABA and with an unknown mechanism of action.

In the International Monotherapy Study Group of gabapentin,[29] bodyweight increase was reported in 5% of 72 patients at a dosage of 300 mg/day and 2.7% in 72 patients at a dosage of 900 or 1800 mg/day. In the US Gabapentin Study[30] it was observed in 6% of 82 patients with different dosages (600, 1200 and 2400 mg/day).

The bodyweight gain observed with the use of gabapentin seems to be related to the prescribed dose: Baulac et al.,[31] in a French collaborative study, observed bodyweight gain in 6, 10 and 15% in a group of 610 adult patients with partial epilepsy who were receiving, 1200 to 1600, 1600 to <2000, and 2000 mg/day, respectively, of gabapentin as add-on therapy. De Toledo et al.[32] reviewed changes in bodyweight in 44 patients treated with gabapentin for a period of 12 months or more. 28 patients were receiving gabapentin at dosages of >3000 mg/day. Ten patients gained more than 10% of their baseline bodyweight, 15 gained 5 to 10%, 16 had no change and three lost 5 to 10% of their initial bodyweight.

3. Mechanisms of Bodyweight Control

The control of bodyweight involves multiple mechanisms. It depends on the balance of caloric intake and expenditure of energy. The hypothalamus is the principal site of integration of information that regulates food intake and energy expenditure.[33] The medial hypothalamic nuclei (ventromedial nucleus, dorsomedial nucleus and paraventricular nucleus) and the lateral hypothalamus differentially regulate food intake: the medial hypothalamic area seems able to inhibit feeding behaviour, whereas the lateral hypothalamic area predominantly activates feeding behaviour. Experimental animals with ventromedial lesions were shown to present hyperphagia and those with lateral lesions, aphagia and bodyweight loss.[34] The hypothalamus receives signals arising from food ingestion and metabolism and social and emotional influences, acting through the brain stem (nucleus tractus solitarius) and the limbic system.[33] Food intake depends on olfactory, oral and somatic sensory input, on input from stomach and intestinal stretch receptors, on some neuropeptides released from the intestinal tract acting through the vagal nerve afferents, and on glucose levels affecting glucose-sensitive neurons in the lateral hypothalamus.

Hypothalamic neurons are also modulated by neurotransmitters, neuromodulators and hormones.[35] Thus, GABA and neuropeptide Y specifically increase carbohydrate consumption and decrease energy expenditure.[36] Serotonin reduces food ingestion by acting through the medial hypothalamus. Low dose serotonin specifically inhibits carbohydrate consumption, whereas higher doses induce a more general suppression of appetite in rats.[37] Injection of norepinephrine (noradrenaline) into the medial hypothalamus elicits a feeding response in satiated rats through an action on α_2-adrenergic receptors,[38] whereas stimulation of β-adrenergic or dopaminergic receptors in the lateral hypothalamus suppresses feeding.[39] Lastly, leptin and glycerol released from adipose tissue may act on lateral hypothalamic neurons. Leptin, exclusively produced by the adipose tissue, signals the amount of

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energy stores and thus provides important feedback information to the brain, which is necessary for the precise regulation of long-term energy balance.[40] It has been shown that *ob*/*ob* mice, which present mutations in the leptin gene, are obese because they fail to produce leptin. Leptin deficiency was then suggested as a cause of human obesity; however, in human obese individuals, leptin levels increase appropriately in response to body adiposity. Verrotti et al.[16] have also shown in obese patients taking valproic acid that elevation of serum leptin levels correlates with the increase in BMI, as in other types of obesity. The fact that obese individuals have elevated serum leptin levels, and that these high levels fail to produce changes in energy intake or expenditure that restore fat mass to normal, has led to the hypothesis of leptin resistance in human obesity, possibly due to deficient hypothalamic leptin receptors.[40] This leptin resistance as a primary cause of obesity, or as a secondary phenomenon that exacerbates the main (unknown) cause, is controversial.[41]

Caloric expenditure depends on basal metabolic rate, thermogenesis and physical activity level. Minor temperature changes in the hypothalamus may explain increased appetite. Basal metabolic rate may be influenced by neurotransmitters such as GABA, as mentioned above, and norepinephrine. Activation of both α- and β-adrenergic receptors enhances basal metabolic rate and thermogenesis.[42] Basal metabolic rate is also influenced by circulating hormones (thyroid hormones, corticotropin) and growth factors (insulin-like growth factors) and by genetic traits, which may be specific to the caloric substrate or to leptin or glucose-responsive neurons.

4. Proposed Mechanisms for Anticonvulsant-Induced Bodyweight Gain

The exact mechanisms of bodyweight gain in patients taking valproic acid remain to be established, but several potential mechanisms have been suggested.

Lowered blood glucose level has been proposed as one mechanism that could lead to obesity with valproic acid therapy. Low glucose level stimulates eating through an effect on glucose-responsive neurons in the medial hypothalamus, which in turn reduce the efferent inhibitory output to the lateral hypothalamus.

The mechanisms by which valproic acid induces a low blood glucose level have been investigated. A decreased binding affinity of serum albumin for palmitate has been found in the serum of valproic acid–treated patients.[43,44] This is due to competition between valproic acid and palmitate for the binding. This could result in increased availability of long-chain fatty acids, which stimulates insulin production, thus increasing lipogenesis, decreasing lipolysis, and lowering serum glucose. Isojärvi et al.[14] have shown that women with obesity taking valproic acid have high levels of fasting serum insulin and low levels of serum insulin-like growth factor-binding protein 1. It has to be noted that hyperinsulinaemia may be responsible for the high rate of women taking valproic acid therapy who are reported to have polycystic ovaries and hyperandrogenism.[14,45] As pubertal and prepubertal girls who gain bodyweight with valproic acid do not have elevated insulin levels according to a study carried out by Rattya et al.,[46] other mechanisms leading to low blood glucose may be involved.

Another possible cause for lowered blood glucose may be the deficiency in carnitine directly caused by valproic acid. The reduction of serum carnitine levels can both reduce β-oxidation of fatty acids[47] and impair gluconeogenesis. The inhibitory effect on gluconeogenesis from lactate, glycerol and alanine is dependent on valproic acid concentration. The decreased β-oxidation of fatty acids, leading to the need for other 'fuels' such as glucose, may explain an increase in glucose consumption. Thus, on the one hand, valproic acid could induce an increased availability of fatty acids, and on the other hand it could indirectly reduce their metabolism, both effects increasing the amount of fat available for deposition in adipose tissue.

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As an alternative hypothesis, valproic acid may increase appetite for carbohydrates and reduce energy expenditure by enhancing GABA-mediated neurotransmission.[36] This action would be related to the increase of GABA-mediated inhibition in the medial hypothalamus, as GABA injections in the hypothalamus have been shown to increase food ingestion.[33] An effect of valproic acid on catecholamine-stimulated thermogenesis has also been hypothesised, but not confirmed.[47]

Lastly, an increased intake of energy-rich beverages had been suggested as a possible explanation for bodyweight gain but this hypothesis was not supported by Breum et al.[47] To summarise, the current proposed mechanisms of valproic acid–induced obesity involve hypoglycaemia that stimulates appetite and increased food intake, coupled to an increase in fatty acid availability.[1]

The mechanisms of bodyweight gain with gabapentin and vigabatrin could also reflect enhancement of GABA-mediated inhibition in the medial hypothalamus. However, it must be noted that another anticonvulsant known to increase GABA-mediated inhibition, tiagabine, actually induces bodyweight loss.[33] These differences could be related to regional variations in the effects of these different anticonvulsants on GABA in the brain.

Bodyweight gain with carbamazepine has been related to water retention. An effect on antidiuretic hormone (ADH) has been suggested but it is more generally accepted that the water retention caused by carbamazepine is an ADH-like effect, because ADH levels are not usually increased.[48] This bodyweight gain is associated with hyponatraemia and serum hypo-osmolality, and clinical examination may show oedema. The study by Perucca et al.[19] confirmed that hyponatraemia and hypo-osmolality may occur during carbamazepine treatment. The incidence of electrolyte abnormalities varies between 7.5 and 33%, respectively, of the treated patients in the studies of Perucca et al.[19] and Henry et al.[20] This can be related to the serum concentrations of carbamazepine, which were lower in the first study, probably because of metabolism induction by other associated anticonvulsants. There is evidence that water intoxication tends to be associated with toxic serum concentration.[19] Even if carbamazepine-treated patients have a normal plasma sodium level and osmolality, their capacity to excrete a water load (excessive intake of fluids) may be grossly impaired.[19]

However, increased appetite and increase of bodyweight without oedema have also been described with carbamazepine therapy.[22] In this case, the bodyweight gain is caused by fat deposition. The mechanisms are unknown, but the chemical structural similarity with tricyclic antidepressant drugs is a possible lead. Indeed, tricyclic antidepressants may cause bodyweight gain, possibly by effects on norepinephrine- and/or serotonin-mediated neurotransmission.[49,50] So it can be hypothesised that carbamazepine could induce fat deposition by similar mechanisms. Lastly, the role of carbamazepine-induced thyroid hormone alterations has been suggested, but is controversial.[22]

5. Clinical Implications

Bodyweight gain in children, adolescents and adults disturb general health, causing cosmetic adverse effects, and can have serious psychological effects. Added to adolescence itself and epilepsy, bodyweight gain may be catastrophic and lead to the withdrawal of the drug. Discontinuation of therapy was observed in 9% of the 55 patients treated with valproic acid in the study of Corman et al.[1]

Bodyweight gain may also play a role in the occurrence of more severe adverse effects such as polycystic ovaries in women taking valproic acid. According to Isojärvi et al.,[21] 80% of the women treated with valproic acid before the age of 20 years had polycystic ovaries and hyperandrogenism. In a second study,[14] these authors evaluated the association between obesity, hyperinsulinaemia, polycystic ovaries and hyperandrogenism in women taking valproic acid (22 patients) or carbamazepine (43) for epilepsy and 43 healthy controls. Obesity was found in 59% of women taking valproic acid, 28% taking carbamazepine and 12% of controls. In 10 (71%) of 14 valproic acid–treated women with polycystic ovaries/hyperandrogen-

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ism, the average bodyweight gain was 22kg (range 8 to 49kg). Conversely, only 1 (13%) of 8 valproic acid–treated women without polycystic ovaries/hyperandrogenism showed an obvious bodyweight gain.

However, these studies reporting an increased risk of polycystic ovary syndrome are not substantiated by other studies.[51,52] Murialdo et al.[52] did not find a higher frequency of this syndrome among valproic acid–treated women, although these women had high levels of serum androgens and a very high percentage of hyperandrogenic anovulation (63.6%). Bauer et al.[17] suggested that the manifestation of polycystic ovary syndrome in patients with focal epilepsy is not related to the administration of valproic acid or carbamazepine. More recently, a number of interesting papers have been published on this controversial topic.[53-55]

6. How to Manage Bodyweight Gain in Patients with Epilepsy

Attention must be given, in the first instance, to diet, even though dietary advice, exercise and use of medications to lose bodyweight are usually ineffective in reducing bodyweight gain.[1,10] Some patients find this approach unacceptable or ineffective and may prefer to try another anticonvulsant. Conversely, when a change of treatment is proposed some patients prefer to continue with the current drug, as their epilepsy is well controlled.

The advantages of long-term valproic acid therapy should be weighed against the risks of bodyweight gain alone or the associated more severe adverse effects. In idiopathic generalised epilepsies, the excellent efficacy of valproic acid seems to outweigh the risks.[53] In partial epilepsies, other effective medications should be considered.

Lamotrigine could be used as an alternative to valproic acid in patients who gain bodyweight. Data from controlled clinical trials of adjunctive therapy with lamotrigine suggest that it does not cause bodyweight gain; however, this outcome has not been evaluated using lamotrigine as monotherapy.[56]

7. Conclusion

Change in bodyweight is frequent with the use of some anticonvulsant drugs. This bodyweight change may interfere with the proper use of these drugs and may pose some significant health risks. Marked bodyweight gain has been reported for valproic acid, carbamazepine, and also with the newer anticonvulsants gabapentin and vigabatrin. Patients starting these medications should be warned of possible bodyweight gain and should be advised to begin diet and routine exercise even if these recommendations are often ineffective. It is also prudent to avoid combinations of valproic acid with other anticonvulsants such as carbamazepine, gabapentin or vigabatrin which can lead to bodyweight gain.

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