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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Weight changes associated with antiepileptic mood stabilizers in the treatment of bipolar disorder

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Abstract

Objective To present up-to-date information and recommendations on the management of body weight changes during the use of antiepileptic mood stabilizers in bipolar disorder to help clinicians and patients make well-informed, practical decisions.

Data sources Umbrella review. Systematic reviews and meta-analyses on the prevention, treatment, and monitoring of body weight changes as a side effect of the mood stabilizers valproate, lamotrigine, topiramate, and carbamazepine were identified in Embase (2010–2015, no language restrictions).

Study selection The search yielded 18 relevant publications on antiepileptic mood stabilizers and weight changes in bipolar disorder.

Data extraction Relevant scientific evidence was abstracted and put into a clinical perspective by a multidisciplinary expert panel of clinicians with expertise in the treatment of bipolar disorders across all age groups and a patient representative.

Results Valproate has been proven to be associated with weight gain in up to 50% of its users, and can be detected 2–3 months after initiation. Carbamazepine has been proven to have a low risk of weight gain. Lamotrigine and topiramate are associated with weight loss. Other option for this sentence = Weigth gain has been proven to be associated with valproate use in up to 50% of its users, and can be detected within 2-3 months after initiation.

Conclusion Each antiepileptic mood stabilizer has specific effects on body weight and accordingly requires a discrete education, prevention, monitoring, and treatment strategy. Clinicians are recommended to adopt an active, anticipatory approach, educating patients about weight change as an important side effect in order to come to informed shared decisions about the most suitable mood stabilizer.

The original version of this article was revised: In the original version of this article unfortunately two tables have been missing. By mistake they have been published as Supplementary Material. We apologize for any inconvenience caused.

Key points
- Weight changes are highly prevalent and an important issue for patients.
- Adopt an active, anticipatory approach, educating patients about weight change as an important side effect.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00228-018-2517-2) contains supplementary material, which is available to authorized users.

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Keywords Bipolar disorder · Weight gain · Weight loss · Anti-obesity agents · Body weight changes · Valproate · Lamotrigine · Topiramate · Carbamazepine

Introduction

Mood stabilizers are first- and second-line treatments in bipolar disorder [1], with antiepileptics like valproate and lamotrigine being prescribed for several indications, such as mixed episodes, insufficient clinical response to lithium, or contraindications for lithium due to renal side effects [2].

As many patients rely on mood stabilizers as a long-term maintenance treatment, optimal harm/benefit ratios are essential. Weight gain can be a serious side effect as it is associated with higher risks of comorbidity and reduced well-being and treatment adherence [3]. Each antiepileptic mood stabilizer has its own specific influence on body weight. For example, while increased appetite and weight gain are especially concerning with the use of valproate [4, 5], these issues are of lesser concern with carbamazepine and lamotrigine. Conversely, topiramate, which is sometimes prescribed in juvenile bipolar disorder, can induce weight loss. Potential weight changes warrant particular attention in bipolar patients given that many already are at higher risk of overweight due to their genetic backgrounds, concomitant medications, and unhealthy life styles [6].

Over the past decades, there has been considerable interest in metabolic dysregulation, obesity prevention, and metabolic screening in general psychiatric practice, particularly in antipsychotic treatment. Current guidelines underline that bipolar disorder and its treatment increase the risk of comorbid medical conditions such as overweight. Routine (at least annual) monitoring of cardiovascular and metabolic indicators is recommended, with a broader check-up for patients with rapid or excessive weight gains [1, 7].

Since treatment guidelines by definition provide general directions, they are not always helpful in finding solutions to individual clinical dilemmas. What to do, for instance, when a patient at high risk of relapse is an excellent responder to valproate but has since been experiencing severe weight gain and is therefore seriously considering to switch treatments? As clinicians, we should consider weight change an important argument in a patient's decision to start or discontinue specific drug treatments.

The objectives of the present study then are to give an overview of the literature about unwanted weight changes associated with the use of antiepileptic mood stabilizers in bipolar disorder and provide a summary and discussion of evidence-based practices for the prevention, monitoring, and treatment of these side effects. Based on these, we will formulate recommendations to guide patients and clinicians in their search for practical solutions to weight changes induced by antiepileptic mood stabilizers.

Methods

This umbrella review was part of a national program on general treatment guidelines for the management of side effects of psychotropic medication for clinical practice in The Netherlands. The main goal of the project was to identify and address clinically important issues concerning side effects that are insufficiently covered in the current treatment guidelines and—if possible—make additional, evidence-based recommendations. In a consensus meeting with clinicians and a patient representative, all members were asked to rank all list of frequent and severe side effects on clinical relevance, based on their clinical experience. Weight change was chosen as the most important adverse effect of antiepileptic mood stabilizers requiring additional recommendations.

We performed a systematic literature search of Embase covering the period between January 2010 and December 2015 (no language restrictions). PRIMSA guidelines (http://prisma-statement.org) were followed; however, we only selected systematic reviews and meta-analyses on the prevention, treatment, and monitoring of weight changes in non-lithium mood stabilizers (i.e., valproate, lamotrigine, topiramate, and carbamazepine; Table 1 (supplement)).

Inclusion criteria we used were (1) only systematic reviews, (2) patients with a psychiatric disorder (e.g., not epilepsy), (3) study on the above-described mood stabilizers, and (4) weight change as an outcome variable. Exclusion variables were (1) patient with pregnancy or post partum (2) topiramate comedication for weight loss induction.

Conclusions based on the evidence presented were subsequently discussed by an expert panel consisting of four psychiatrists (1 child, 2 adult, and 1 geriatric psychiatrist), a pharmacist, a physician assistant, a postdoctoral psychologist, and a patient representative. The experts were selected on their clinical and scientific profile and are all working with patients with bipolar disorder of all ages, in mental health institutes or (academic) hospitals. Relevant considerations were discussed and put into perspective, which resulted in a set of supplementary recommendations, after which the proposed recommendations were presented to clinicians countrywide for comments, feedback, and approval.

Results

The search yielded 18 relevant publications on antiepileptic mood stabilizers and weight changes in bipolar disorder [8–25]. The most relevant conclusions from these reviews are presented in Table 1. Valproate has been proven to be associated with weight gain in up to 50% of its users, and can be detected 2–3 months after initiation. Carbamazepine

Table 1 Conclusions regarding antiepileptic-induced weight changes as derived from recent systematic reviews and meta-analyses

No.	Drug	Conclusion	Level of evidence*	References
1	Valproate	Valproate has been proven to be associated with weight gain in up to 50% of its users, with reported gains ranging between 1 and 14 kg.	1	[7–13]
2	Valproate	Women using valproate have been shown to gain more weight than men.	1	[9, 14, 15]
4	Valproate	There are indications that particularly in children and adolescents weight gain more often occurs in early valproate treatment and tends to plateau in the later stages of treatment.	3	[15, 16]
5	Valproate	There are indications that in adults weight gain can occur 2 – 3 months after starting the drug and that gains may continue in longer-term treatment.	3	[7, 15]
6	Valproate	There are indications that children/adolescents are no more at risk of weight gains than adultsadults and elderly people.	3	[15, 16]
7	Valproate	There are tentative indications that there is no dose-response relation between valproate and weight gain.	3	[15]
8	Lamotrigine	Lamotrigine has been proven to have a low risk of weight gain.	1	[7, 9, 11, 12, 17, 18]
9	Lamotrigine	There are indications that lamotrigine may induce weight loss.	3	[19]
10	Topiramate	Weight loss and reduced appetite are dose-dependent and more serious in topiramate doses >= 200 mg/day.	1	[20]
11	Topiramate	There are indications that in children topiramate-induced weight loss is not dose-dependent.	3	[21]
12	Topiramate	Topiramate has been proven to be associated with weight loss in 5-81% of its users and decreases appetite in 5-24%.	1	[11, 12, 20, 22, 23]
13	Carbamazepine	Carbamazepine has been proven to have a low risk of weight gain.	1	[7, 9, 11, 12]
14	Metformine	Metformine has been proven to be the most effective pharmacological treatment of weight gain in bipolar disorder.	1	[24]

*Levels of scientific evidence according the Dutch evidence-based guideline development (EBRO) criteria (26). (Level 1= systematic review or at least two independent randomised, double-blind, comparative clinical trials of good quality and sufficient sample size ; level 3 = one comparative study.)

has been proven to have a low risk of weight gain. Lamotrigine and topiramate are associated with weight loss. The flow diagram is presented in figure 1 [supplement].

Our expert panel discussed the results, which were converted into clinical practice recommendations that are described in Table 2. Clinicians are recommended to adopt an active, anticipatory approach, educating patients about weight change as an important side effect in order to come to informed shared decisions about the most suitable mood stabilizer.

Table 2 Clinical recommendations for management of antiepileptic-induced weight changes in the treatment of bipolar disorder

Prevention

1. When considering antiepileptic mood stabilizers as the treatment of choice, always take the risk of weight change into account. This is especially important for patients with other risk factors for weight gain such as obesity, female sex, old age and weight-inducing comedication. Note that patients may differ in the extent to which they consider weight changes a significant problem.
2. Discuss the prevalence and risks of weight changes with patients *before* starting valproate.
3. Discuss the feasibility and burdens of lifestyle management to patients at higher risk of weight gain.
4. The preventive prescription of medication for weight loss (e.g. metformin) is not recommended. Medication to counter weight gain (e.g. metformin) should be exclusively reserved for patients in whom weight gain has occurred.
5. Consider whether weight gain may (also) be induced by comedication and consider switching the comedication to a class of drug that is not or less associated with weight gain (e.g. antipsychotics)
6. When considering topiramate, discuss the risk of weight loss with the patient, especially in the case of juvenile and elderly patients.

Monitoring

7. Measure the patient's weight at baseline, within 4–6 weeks of treatment with valproate and topiramate or sooner if clinically indicated, and then once every 6 months.
8. Measuring weight is not the best way to screen for metabolic changes. It is recommended to calculate BMI in juvenile patients and to consider measuring the waist circumference in elderly patients.
9. Annual metabolic screening is recommended in patients on valproate and topiramate maintenance treatments.
10. Metabolic screening is indicated with body weight / BMI changes in excess of 7%.

Treatment

11. Targeted pharmacological treatment for weight loss is optional. Metformin is recommended as the first choice treatment We do not recommended standard preventive use of metformin.

12 Behavioural therapy, physical exercise programmes and lifestyle changes may be considered for patients on mood stabilizers.

Discussion

Both patients and clinicians have indicated that potential weight change can be a relevant factor in the choice of mood-stabilizing medications. However, although antiepileptic mood stabilizers each have specific effects on body weight, each requiring distinct education, prevention, monitoring, and treatment strategies, most treatment guidelines do not prioritize weight change and routine monitoring of body weight. Whether the risk of weight change is taken into consideration most often depends on the treatment phase and patient preferences. In the initial phase (e.g., with acute mania), efficacy is often emphasized over potential side effects such as weight change based on the notion that the management of weight gain or loss will only become relevant in the longer term (maintenance treatment).

Based on the evidence, we suggest a more proactive approach when it comes to the choice of mood stabilizers in the treatment of bipolar disorder in that we recommend to discuss the possible side effects of the antiepileptics valproate, lamotrigine, topiramate, or carbamazepine with the patient in advance. Shared decision-making should in this context entail the clinician providing the patient and significant other(s) with relevant drug information, informing the patient about the risks and benefits of the agent(s) under consideration, an evaluation of the patient's ideas about body weight changes and discussion of patient-specific risk factors. We moreover suggest to start body weight monitoring much earlier than most guidelines advise given that weight changes are already detectable after 4–6 weeks, with subsequent weight checks every 6 months to allow for the possibility that some patients may want to consider other treatment options in case of unacceptable weight changes. We recommend future research on mood stabilizers in bipolar disorder to take into account the patients' perspective on weight change.

There are several other topics and limitations we need to address. First, given that systematic research on weight monitoring strategies was absent, we based our monitoring recommendations on clinical expertise and the available evidence of weight change mechanisms. The evidence for strategies to prevent weight change (especially weight gain) was limited. With little evidence for the effectiveness of preventive medication, such as metformin, we, however, think the risk/benefit ratio is suboptimal in view of the potential side effects and drug-drug interactions reported. Therefore, we did not recommended the preventive use of metformin; the drug may be considered if (significant) weight gain has occurred.

Research has yielded more information on the manifestations and management of antipsychotic-induced changes in body weight. Here, both pharmacological and non-pharmacological therapies were shown to be moderately effective in the prevention and treatment of weight gain [26, 27]. As many patients with bipolar disorder use combinations of mood stabilizers and antipsychotics whose mechanisms may partially overlap, these findings may also be relevant for the current patient population and their treatment.

As to the question whether weight changes are dose-dependent, findings are also limited. For valproate, weight gain does not appear to be dose-dependent [4], while for lamotrigine, weight loss appears to be associated with higher doses only. The evidence for the dose dependency of weight loss in topiramate is conflicting: Shamliyan et al. found no dose dependency in a sample of children [22], whereas a dose-dependent relation between topiramate and weight loss was found in the sample of Deaton and Mauro [21].

While differences in the risk profiles for weight change of different mood stabilizers merit attention, the fact that mood stabilizers, lithium, and antipsychotics are not necessarily interchangeable also warrants attention. Although carbamazepine and lamotrigine show a better weight change profile, the indications for their prescription vary (treatment of manic/depressive phase or mixed features), as do their efficacy and other side effects (e.g., Steven-Johnson syndrome in lamotrigine and adverse cognitive effects associated with carbamazepine).

In conclusion, weight change, especially weight gain in the case of valproate, can have a major impact on patients' lives. Besides being a psychological burden, weight gain also is an important risk factor for metabolic dysregulation, which is why bipolar patients always need to be informed of this important side effect before reaching a shared decision on the use of antiepileptic mood stabilizers.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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