

Zonisamide in the Treatment of Obesity: A Meta-Analysis

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ABSTRACT

Incidence of obesity continues to rise worldwide with each year especially in developed countries. On the other hand success achieved with pharmacotherapy of obesity is disappointing, with some of the unmet needs in management strategies for obesity. Zonisamide an anti-epileptic drug has been found to have significant weight reduction properties with favorable safety profile. Present meta-analysis has been done with the aim of analyzing the efficacy of zonisamide in obesity. Electronic data bases were searched for all types of studies related to use of zonisamide in obesity and binge eating disorder. Change in body weight following treatment with zonisamide was the primary outcome measure analyzed. Both fixed and random effect models were used for statistical analysis of the data. With total 111 patients analyzed from 3 eligible studies; a significant reduction in weight from baseline by 5.88 kg (MD: -5.88; 95% CI:-7.51 to -4.25) at 16 weeks could be expected by treatment with zonisamide. As the data on safety profile of zonisamide especially long term was either incomplete or not available, analysis of safety profile was not carried out. Future studies analyzing the efficacy and long term safety of zonisamide on large population and for long term are preferred.

INTRODUCTION

Obesity is considered as a metabolic and neuroendocrine disorder associated with complications like Type 2 Diabetes Mellitus (DM), Hypertension, Coronary Artery Disorders, Osteoarthritis, certain types of cancers, etc (Guaraldi *et al.*, 2011 and Glandt *et al.*, 2011). By definition, a person is identified as 'obese' when Body Mass Index (BMI) is ≥ 30 kg/m² and as 'over weight' when BMI is ≥ 25 -29.9 kg/m² (Glandt *et al.*, 2011). Incidence of obesity continues to rise worldwide with each year especially in developed countries (Glandt *et al.*, 2011). On the other hand success achieved with pharmacotherapy of obesity is disappointing, with some of the unmet needs in management strategies for obesity. Pharmacotherapy alone is not as effective as diet and life style modifications (Bray 2008).

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Successful weight loss strategy in obesity needs multiple approaches ranging from diet and life style modification, behavioral therapy along with pharmacotherapy as a means to enhance the rate and amount of weight loss (Seagle *et al.*, 2009). A baseline weight loss of 5%-10% at the end of 6-12 months from a pharmacological agent is necessary to observe beneficial effect in terms of decrease in obese related complications (Glandt *et al.*, 2011 and Witkamp 2011). American College of Physicians (ACP) guidelines recommends diet and life style modification in all patients and addition of pharmacological therapy with anti-obesity drugs for those who fail to attain the target weight loss. Surgical approaches are recommended for patients with BMI ≥ 40 kg/m² (Glandt *et al.*, 2011). National Institute of Health (NIH) of USA suggests that even over weight patients with BMI ≥ 27 kg/m² with risk factors like cardiovascular disorders and diabetes need long term pharmacological therapy. Similarly, surgery is recommended in such high risk patients with BMI ≥ 35 kg/m². NIH also recommends the weight loss goal of more than 2kg in first month, weight loss of

at least 5% from baseline value at the end of 6-12 months treatment with the pharmacological therapy (Glandt *et al.*, 2011). In patients not responding to weight loss after 3 months of continuous treatment, pharmacotherapy is better discontinued (Hainer 2011). Food and Drug Administration (FDA) of USA has criteria for approval of new anti-obesity drugs recommending that a pharmacological therapy to be approved needs to reduce $\geq 5\%$ of weight loss from baseline in at least 35% of total treated patients (Witkamp 2011). In addition, drug is also supposed to show improvement in biomarkers like blood pressure, lipid levels and glucose levels (Powell *et al.*, 2011).

The major unmet needs in the area of pharmacological treatment of obesity are poor compliance, lesser rate and amount of weight loss, regain in weight after the stopping drugs, lack of safety data for long term therapy and scarcity of research on how to maintain achieved weight loss (Seagle *et al.*, 2009; Halpern *et al.*, 2010) Like hypertension and Type 2 DM, obesity is also considered as chronic disorder and needs both pharmacological and non-pharmacological approaches and lifelong treatment with combination of at least two drugs to achieve clinically significant weight loss (Witkamp 2011; Halpern *et al.*, 2010 and Ioannides-Demos *et al.*, 2011). Long term maintenance of achieved weight loss is also equally important in order to observe clinical benefits in terms of decrease in obesity related complications (Bray 2008). At present orlistat an intestinal lipase inhibitor is the only drug that is being approved for long term therapy. Earlier, sibutramine was another drug which enjoyed this status before its recent ban due to its association with increased incidences of cardiovascular related adverse drug reactions (Witkamp 2011, Powell 2011). With the association of orlistat with hepatotoxicity as adverse drug reaction on long term use, review on its long term use is also possible (Ioannides-Demos *et al.*, 2011). Apart from these unmet needs in pharmacological treatment with anti-obesity drugs, clinical trials on anti-obesity drugs are also hindered by the selection of appropriate parameter to evaluate their beneficial effects (Ioannides-Demos *et al.*, 2011).

Considering the demand for anti-obesity drugs and with the advent of new targets, list of future candidate drugs and combinations of presently available drugs as anti-obesity drugs is also growing (Witkamp 2011). One such agent is zonisamide and its combination with bupirone. Observation that zonisamide has adverse drug reaction of weight loss in epileptic patients was the basis for its testing as anti-obesity drug. As a single drug, zonisamide was later proved to have significant effect on weight loss in obese patients in randomized controlled trials (Gadde *et al.*, 2003). Present study was conducted with the aim to analyze short term benefits of zonisamide as anti-obesity drug.

MATERIALS AND METHODS

Eligibility criteria

Studies with any type of study design and duration, comparing treatment of zonisamide with control group on obese (BMI ≥ 30 kg/m²) or over weight (BMI: ≥ 25 - 29.9 kg/m²)

patients of either sex aged above 18 years were eligible for inclusion.

Search methodology

Two authors independently conducted electronic data search for the relevant articles in MEDLINE, Cochrane library The Cochrane Register for Controlled trials and SCIRUS including conference proceedings with MeSH terms 'zonisamide' and 'obesity'; 'zonisamide' and 'over weight'; 'zonisamide' and 'binge eating disorder' separately. Manual search of bibliographies of the meta-analysis, published trials, and other relevant articles was also carried out. We limited our search to those studies published between 1990 to October 2011 in English literature.

Data extraction

Published data independently extracted by two authors was considered for the analysis after achieving consensus by two authors. Changes in the weight measured either in BMI or 'Kg' from baseline was collected for analysis. Data were extracted from three studies meeting eligibility criteria (Gadde *et al.*, 2003; Mc Elroy *et al.*, 2006 and Ricca *et al.*, 2009). Unlike other two eligible studies where required mean and Standard Deviation (SD) were published and directly extracted; in study by Gadde *et al.*, 2003 Standard Error (SE) was published. For this study, we calculated the SD from published SE. Data extracted from study by Ricca *et al.*, 2009 was of at the end of 24 weeks and from studies by Gadde *et al.*, 2003 and Mc Elroy *et al.*, 2006 was of at 16 weeks though the follow up data up to 32 weeks in Gadde *et al.*, 2003 and 12 months in Ricca *et al.*, 2009 were available. This was done with the intent to analyze short term treatment effects of zonisamide. So our result of change in weight as SMD can be considered as pooled analysis at 6 months rather not by specific time point.

Outcome measures

Change in the body weight from baseline at the end of treatment or study period was the primary outcome measure analyzed. We also planned to analyze effects of zonisamide on binge eating frequency from the data of studies by Mc Elroy *et al.*, 2006 and Ricca *et al.*, 2009 However as the data required for the analysis was incomplete for analysis from the study by Ricca *et al.*, 2009 we could not analyze the same.

Statistical methods

Considering the different scales used in different studies to analyze the treatment effect on weight; Standardized Mean Difference (SMD) was the effect measure used to estimate the change in weight at the end of treatment. Both fixed and random effect models were used for statistical analysis of the data. Mantel-Haenszel fixed effect model was used for interpretation and discussion of results. For the same reason no other sub-group analysis, sensitivity analysis or post hoc analyses were performed. Though number of studies included was three, Cochrane Q test for heterogeneity and I² test were used for analyzing inter-trial heterogeneity. A chi square test with P value < 0.10 and I² test

value >50% was considered as an indicator of significant heterogeneity. Due to high chances of errors associated with the use of SMD as effect measure, analysis of change in the weight in terms of 'Kg' was also done by analyzing data from two studies. Mean Difference (MD) using Mantel-Haenszel fixed effect model was used for calculating change in body weight in terms of 'Kg'. RevMan software version 4.3.2 by Cochrane collaboration was used for statistical analysis of the data.

Quality evaluation and publication bias

Eligible studies were assigned a maximum possible score after subjecting them to structured review for quality evaluation as described by Nancy and Robert (Nancy and Robert 2002). The unblinded quality assessments of published information were independently performed by two co-authors and then a consensus was achieved on the final score. Publication bias was not analyzed as number of studies included under analysis was less.

RESULTS AND DISCUSSION

Search results

We got total 1251 references, our search yielded 169 relevant articles of which 1 was meta-analysis, 4 were randomized controlled studies, 2 were retrospective studies and 5 were prospective studies. Remaining were reviews and miscellaneous articles on obesity and its management. One prospective controlled study and two out of four randomized studies met the eligibility criteria and were included for analysis (Gadde *et al.*, 2003; Mc Elroy *et al.*, 2006 and Ricca *et al.*, 2009). Study by Yoon *et al.*, 2008 was published as abstract with no data available for extraction. We requested the author through mail for the journal citation to avail full text article but ended with no reply. Another was study by Gadde *et al.*, 2007 comparing combination of zonisamide and bupropion with zonisamide. As both the group received the zonisamide, study was not eligible for analysis.

Demographic and clinical characteristics of included studies

The baseline demographic and clinical features of the patients included in three eligible studies are shown in Table.1. Majority of the patients in all the studies were female (>75%) with mean BMI >35 kg/m². Total number of patients who completed study period in Mc Elroy *et al.*, 2006 was 30 out of 60 (50%) at 16 weeks; 30 out of 52 (57.7%) in Ricca *et al.*, 2009 at 24 weeks and 51 out of 60 (85%) in Gadde *et al.*, 2003 at 16 weeks. The drop-out rate was significant in first two studies for reasons mainly due to difficulty in protocol adherence followed by adverse effects and loss of efficacy. However no statistically significant differences in the reasons for and features of drop-out patients and tested patients were found in these studies.

Randomization, blinding and follow-up

In all the three studies data on number of patients who completed the study and data on dropout rate with reasons for drop out was available. Study by Gadde *et al.*, 2003 was double

blinded for initial phase of 16 weeks and later single blinded for another 16 weeks in extension phase. Study by Mc Elroy *et al.*, 2006 was double blinded and that by Gadde *et al.*, 2003 unblinded. Study by Gadde *et al.*, 2003 had mentioned about randomization method followed but no such information was available from study by Mc Elroy *et al.*, 2006 Study by Ricca *et al.*, 2009 was controlled non-randomized study. Except study by Gadde *et al.*, 2003 other two studies were basically conducted on patients with binge eating disorder (BED) with the aim to analyze effects of zonisamide on binge eating frequency along with changes in body weight.

Interventions

With regard to interventions, there was a major difference in the dose of zonisamide used in study by Ricca *et al.*, 2009 compared to other two studies. The mean dose and duration of zonisamide administration was 25-150mg/day for 24 weeks by Ricca *et al.*, 2009; 100-600 mg/day for 16 weeks by Mc Elroy *et al.*, 2006 and Gadde *et al.*, 2003 for 32 weeks. Though the dose of zonisamide used was low in Ricca *et al.*, 2009 compared to other two studies; it was the only study in which patients in both the group also received cognitive behavioral therapy (CBT) for BED in addition. Study by Gadde *et al.*, 2009 was the only study to include diet and life style counseling in all patients and this was the only study to analyze effects of zonisamide on weight changes in patients with obesity or over weight without BED. Other two studied were basically analyzed both changes in body weight and binge eating frequency. In all the studies the dose of zonisamide was gradually increased on weekly basis.

Results of outcome measure

With total 111 patients who completed the study period (non- Intention To Treat (ITT) design) analyzed from 3 eligible studies; a significant reduction in body weight from baseline was observed in zonisamide treated group (SMD: -1.90; 95% CI: -2.39 to -1.42). A chi square test for heterogeneity with p value 0.24 and I² test value of 29.2% was recorded indicated mild intertrial heterogeneity (Fig.1). As the data on changes in weight after treatment with zonisamide were not available from the study by Ricca *et al.*, 2009 separate analysis of changes in body weight in terms of 'Kg' as parameter performed from the data of studies by Mc Elroy *et al.*, 2006 and Gadde *et al.*, 2003 revealed that zonisamide decreases body weight by 5.88 kg (MD: -5.88; 95% CI: -7.51 to -4.25) at 4 months (Fig.2). Treatment effect from the data of the patients of ITT design revealed body weight loss of 4.53Kg in zonisamide treated group (MD: -4.53; 95% CI: -5.90 to -3.16) at 4 months.

Results of quality evaluation

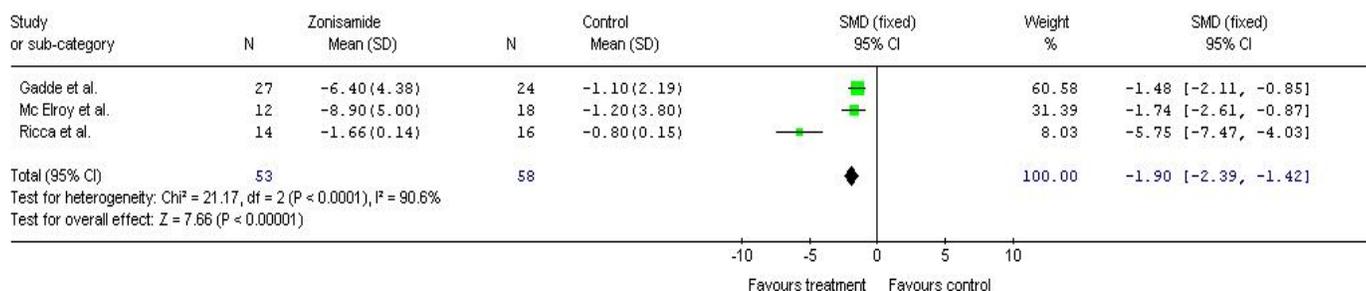
The percentage of maximum possible scores for both the randomized studies by Gadde *et al.*, 2003 and Mc Elroy *et al.*, 2006 was 87.87%. Non-randomized controlled study by Ricca *et al.*, 2009 scored 75.75%.

Table 1: Baseline demographic and clinical features of studies included in analysis.

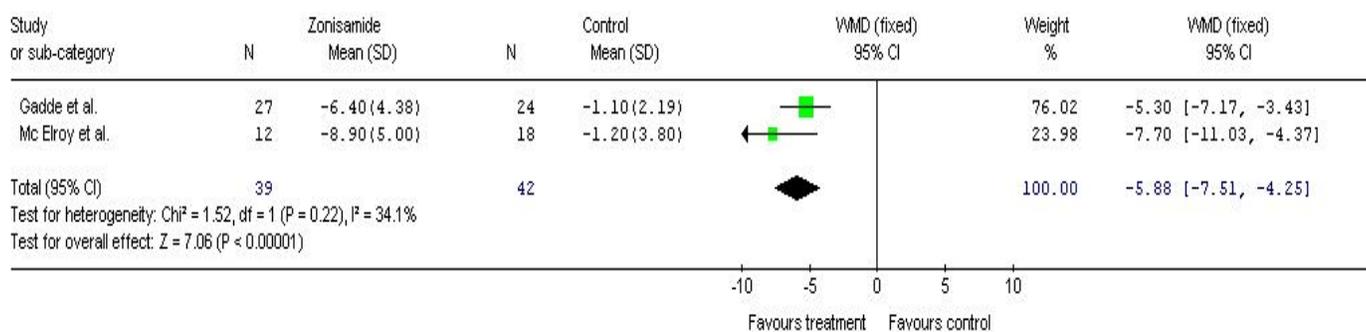
Study	Gadde <i>et al.</i> , 2003		Mc Elroy <i>et al.</i> , 2006		Valdo Ricca <i>et al.</i> , 2009	
	Zonisamide Group (mean ± SE)	Control Group (mean ± SE)	Zonisamide Group (mean ± SD)	Control Group (mean ± SD)	Zonisamide Group (mean ± SD)	Control Group (mean ± SD)
Age(Years)	37.5 ± 1.3	36.4 ± 1.6	44.8 ± 9.3	43 ± 10.7	36.07 ± 11.56	34.8 ± 11.09
Gender(M&F)	5&25	0&30	3&27	4&26	5&23	4&20
Weight (Kg)	98.2 ± 2.5	97.8 ± 2.6	118 ± 30.7	112.8 ± 24.3	N/A	N/A
BMI(kg/m ²)	35.4 ± 0.7	37.2 ± 0.8	42.7 ± 9.5	40.6 ± 7.6	38.43 ± 5.70	39.22 ± 7.84

M: Male; F: Female, BMI: Body Mass Index, N/A: Not Available

Review: Zonisamide in treatment of obesity: A Meta-analysis
 Comparison: 01 Weight loss
 Outcome: 01 Weight loss

**Fig. 1:** Forest plot showing results of weight loss by zonisamide SMD as effect measure.

Review: Zonisamide in treatment of obesity: A Meta-analysis
 Comparison: 01 Weight loss
 Outcome: 01 Weight loss in Kg (Non-ITT)

**Fig. 2:** Forest plot showing results of weight loss by zonisamide in terms of 'Kg' as measure.

DISCUSSION

Interesting feature of zonisamide weight reduction effects is its efficacy in reducing more than 5% of body weight within short period of 4 months with minimal side effects. Unlike other anti-obesity drugs, cessation of zonisamide is not associated with rebound weight gain (Ricca *et al.*, 2009). The clinical implications of these findings are significant as it is found that the intermittent pharmacotherapy of obesity with drugs like sibutramine and phentermine is as equally effective as continuous treatment with advantage of reduced side effects and cost (Hainer 2011). In addition, studies on zonisamide reveal that it has dose and duration dependent effect on weight loss without serious adverse drug

reactions, even after at least one year of continuous treatment (Gadde *et al.*, 2003). As lifelong treatment is preferred in obesity, following intermittent treatment regimen with maximum tolerated dose for long term period or lifelong with reasonable safety profile may become possible with zonisamide. Considering the dose dependent effects of zonisamide, individualization of the dose or duration of treatment can also be preferred depending on severity of obesity. Zonisamide appears to be as effective as presently available anti-obesity drugs. However, its added advantage of reducing binge eating frequency is not as strongly supported as are those for weight reducing effects (Mc Elroy *et al.*, 2006 and Ricca *et al.*, 2009). The added advantages of decrease in blood pressure, improvement in blood glucose and lipid parameters are also

observed in patients treated with zonisamide (Gadde *et al.*, 2003). Since centrally acting anti-obesity agents are supposed to have more weight reducing effects compared to other agents, the interest in new drugs from this class is naturally more even though their adverse reaction profile is not attractive (Witkamp *et al.*, 2011). Zonisamide is centrally acting agent affecting both noradrenergic and serotonergic neurotransmission has shown similar beneficial effects as that of currently available centrally acting agents. Though its exact mechanism of action is clearly not known, it is supposed to act by multiple mechanisms like increasing serotonin release and synthesis, increasing dopamine synthesis, stimulating dopamine D2 receptors and inhibition of carbonic anhydrase activity in the brain feeding and satiety centers (Gadde *et al.*, 2003).

Incidence of serious adverse reactions with previously available centrally acting anti-obesity drugs has led to their ban or restricted use (Witkamp *et al.*, 2011 and Powell *et al.*, 2011). From this perspective, zonisamide appears to be the safe and effective centrally acting anti-obesity drug without serious adverse effects. As an anti-epileptic drug, the major serious adverse drug reactions observed with zonisamide on long term treatment were increased incidence of renal calculi, serious hematologic events, depression etc (Gadde *et al.*, 2003 and Wang *et al.*, 2008). Though the number of studies and data available on zonisamide on its safety in obese patients is less, the major adverse drug reaction observed from presently available studies was small rise in serum creatinine level. The amount of rise in serum creatinine observed was below normal range but significantly different from control group. Implication of this adverse event appears to be insignificant in patients with normal renal function. Incidences of psychiatric adverse reactions like depression with zonisamide may call for its restricted use in patients with mood disorders (Wang *et al.*, 2008).

Pharmacotherapy with combination of anti-obesity drugs is hindered by higher rates of adverse drug reactions. Some of the combinations that proved to be more effective but later led to their withdrawal or ban because of their serious adverse effects are topiramate-taranabant and fenfluramine-phenteramine (Witkamp *et al.*, 2011 and Ioannides-Demos *et al.*, 2011). Combination of zonisamide and naltrexone, the first zonisamide combination has shown favorable results in early phases of clinical trial (Powell 2011). However FDA has declined to approve drug and has asked for the long safety data with this drug combination (Pollack 2011). Another zonisamide combination that is showing promising benefits and hopefully acceptable safety profile is combination of zonisamide and bupirone (Powell *et al.*, 2011 and Halpern *et al.*, 2010). Completed phase 2 study reports favorable efficacy and safety profile with this combination. Though the combination had high dropout rates, added advantage to their synergistic effects on weight reduction effects is the opposite spectrum of the major side effects of zonisamide and bupirone. A randomized study proved that combination of zonisamide and bupirone has same adverse drug reaction profile as that of zonisamide alone with better weight reduction efficacy (Gadde *et al.*, 2007).

However as with other drugs and drug combinations as long as data on long term safety profile of zonisamide or its new combination with bupirone is not available, the hope and scope of the this combinations remains to be observed. Our study has certain limitations. We restricted our search to published studies and also to those published in English literature only. The number of studies and patients analyzed is less.

Only two randomized studies are presently available. As the data on safety profile of zonisamide especially long term was either incomplete or not available, analysis of safety profile was not carried out. Like all anti-obesity drugs, the available data on safety profile of zonisamide is of short duration and on small sample size. Future studies analyzing the efficacy and long term safety of zonisamide on large population and for long term are preferred. It seems that the future studies on anti-obesity drugs will be more and more concentrated on the combination of existing drugs rather than newer and single drugs.

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