Original Research Article

Relationship between the use of drugs and changes in body weight among patients: A systematic review and meta-analysis

Tauqeer Hussain Mallhi[1]*, Iram Ijaz[2], Yusra Habib Khan[2], Amna Javed[1], Umda-tun-Nisa Saleem[1], Raja Ahsan Aftab[3], Abdulaziz Ibrahim Alzarea[2], Nasser Hadal Alotaibi[2], Abdullah Salah Alanazi[2], Muhammad Salman[4], Muhammad Hammad Butt[5]

[1]Department of Clinical Pharmacy, College of Pharmacy, Jouf University, Sakaka, Al-Jouf, Kingdom of Saudi Arabia, [2]Institute of Pharmacy, Lahore College for Women University, Lahore, Pakistan, [3]Faculty of Health and Medical Science, Taylor's University, 47500, Subang Jaya, Malaysia, [4]Department of Pharmacy Practice, Faculty of Pharmacy, The University of Lahore, [5]Faculty of Pharmacy, University of Central Punjab, Lahore, Pakistan

*For correspondence: **Email:** thhussain@ju.edu.sa, tauqeer.hussain.mallhi@hotmail.com; **Tel:** +966-552635200*

Abstract

Purpose: To investigate the impact of drugs on the body weight of patients.

Methods: All the randomized controlled trials that evaluated the impact of medications on the body weight of patients were searched in various databases. Studies quantifying the impact of drugs on body weight when compared to placebo or any other treatment were considered for this review. Moreover, the quantitative synthesis of evidence was also performed by generating the forest plot.

Results: A total of 20 studies involving 18,547 participants were included in the current review. Weight gains ranging from 0.5 to 2.6 kg were associated with the use of pioglitazone, espindolol, brexpiprazole, glimepiride and ezogabine while weight loss ranging from 1.1 to 12 kg was linked with the use of betahistine, naltrexone, bupropion, liraglutide, phentermine, topiramate, orlistat, zonisamide, duloxetine, semaglutide, metformin and linagliptin. The quantitative synthesis suggested that drugs can significantly reduce body weight by -0.53 kg (CI 95 % -1.01, -0.04, p < 0.04) when compared to standard treatment.

Conclusion: The findings of this review suggest substantial association of drugs and weight change during pharmacotherapy. Pioglitzone, brexpiprazole, espindolol, ezogabine and glimepiride cause weight gain while naltrexone, bupropion, betahistine, topiramate, phentermine, zonisamide, semaglutide, linagliptin, liraglutide, orlistat, duloxetine and metformin were associated with weight loss. Drug-induced changes in body weight might cause serious consequences and should be addressed before initiating treatment.

Keywords: Drugs, Weigh change, Weight gain, Weigh loss, Pharmacotherapy

INTRODUCTION

Obesity is one of the most important public health concerns around the globe [1]. According to a recent estimate, 1.9 billion adults aged $\geq$18 years were found to be overweight in 2016. Of these, 650 million adults were stratified as obese [2]. The prevalence of obesity was 42.4 % in U.S adults including 42.1 % for females and 43.0 % for males in 2017 - 2018 [3].

Obesity increases the risk of chronic diseases and leads to considerable morbidity and mortality in developed countries [4-7]. Various environmental, social, genetic, and biological factors influence energy intake as well as energy expenditure [7]. However, it is pertinent to mention that various prescription drugs also cause changes in body weight such as weight gain or loss. Drugs induced changes in body weight are multifactorial and primarily associated with increased appetite (e.g., corticosteroids) or reduced metabolic rate (e.g., beta-adrenoceptor blockers) [8].

Although weight change due to drugs is a potential risk for various complications, these drugs are still being used for a long time in the management of various chronic diseases. It is important to note that drugs induced weight change may also cause non-compliance and is associated with poor quality of life among users. However, these hazards can be controlled to an optimal extent by understanding factors underlying the weight changes and modifying treatment plans which could be translated to improved quality of life and reduced propensity of adverse events among patients [9].

There is a dire need to ascertain the impact of drug therapy on weight changes among patients. The purpose of the current review was to quantify weight changes among patients due to prescribed drugs. The findings of the current study will provide pivotal information to healthcare professionals to individualize treatment decisions. Moreover, these results will aid health authorities in formulating treatment guidelines along with the management of drug therapy-related adverse events.

METHODS

Search strategy and information sources

Studies were searched by three reviewers (II, AJ, UTN) independently using electronic databases. The search strategy was applied to PubMed, Elsevier, ProQuest, Scopus, EBSCOhost, JAMA, ScienceDirect, Ovid, EMBASE, MEDLINE and Google Scholar databases from 2000 to 2020. Reference list of included studies were also screened to identify potentially relevant research articles. Additionally, references of relevant systematic reviews were used for identification of randomized controlled trials (RCTs). Combination of following search terms were used with appropriate operators: "drug(s)", "medication(s)", "weight change", "obesity", "body mass index (BMI)", "weight gain", "weight loss", "overweight" and "underweight". The literature search was limited to only peer reviewed RCTs and was limited to human studies published in English language.

Inclusion criteria

The inclusion criteria were clinical trials involving participants aged between 18 to 75 years, using drugs for at least 1 month, had comparison of drugs with placebo or an alternative drug, regardless of the dose and frequency. The trials investigating quantitative changes were included.

Exclusion criteria

The studies in which changes in body weight was self-reported by the patients, and trials on specialized patients i.e., pediatrics, geriatrics, pregnant and lactating women were excluded from this review. Studies conducted on patients with significant thyroid or immune disorders and patients with Type I diabetes mellitus were also excluded on account of well-documented evidence on disease-related weight changes. Moreover, studies conducted on patients with prior liposuction, previous surgical treatment for obesity, obesity due to known genetic reason, pitting edema, renal disease, active liver disease, uncontrolled hypertension, and carotid revascularization within 14 days before randomization were also excluded from this review. The studies conducted on patients using oral glucocorticoids or estrogen containing contraceptive were also excluded on account of evidence-based weight changing effects. Moreover, studies including alcohol or drug abuses, and serious or unstable patients were excluded to avoid confounded impact of these conditions on weight change. All other study designs except RCTs were also excluded from the qualitative and quantitative analysis of this review.

Data extraction

Initially, titles and abstracts of each study were independently screened by three authors. Articles deemed potentially eligible were retrieved for full-text screening carried out

independently by two investigators. Data regarding demographics of participants (age, gender, mean weight and BMI), duration, study sample size, interventions received (dose and frequency) and measure of outcome were extracted by using a piloted data collection form. All the data collected were tabulated and interpreted.

Study selection

Initially, 51 studies were identified and considered potentially relevant. Out of these, 31 studies were excluded due to various reasons (Figure 1). Twenty studies meeting the predefined inclusion criteria were included in this review. Figure 1 shows PRISMA diagram of study selection procedure.
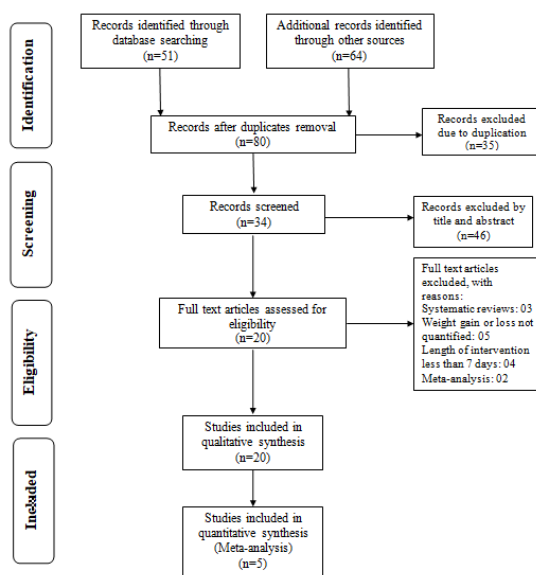
Figure 1: Flow diagram of study selection (PRISMA diagram)

Quality assessment

The methodological quality of included studies was independently assessed by two authors. The adequacy of RCTs was evaluated on the basis of concealment of randomization, blinding and reported outcomes (Table 1). The risk of bias (RoB) within each study was assessed using 7-items checklist.

Quantitative data synthesis

Quantitative synthesis or meta-analysis was considered using REVMAN-5 software. Data extraction was performed by using a piloted data collection tool. Continuous variables were analyzed using weighted mean difference (WMD)

with 95 % CI. The I^2 statistic was used to assess heterogeneity across the studies. A fixed effect model was used when $I^2 < 50$ %, which indicated heterogeneity. However, a random effect model was used if $I^2 > 50$%, after consideration of the potential sources of heterogeneity.

RESULTS

A total of 20 RCTs involving n = 18547 participants (sample size range: 35 – 3876 patients) were included in this review. Quality assessment of included studies was performed against concealment of randomization, stopping trial at an early phase, blinding, and outcomes reporting. All the studies were found to have quality standards to draw firm conclusions from the findings (Table 1). The study duration of included trials ranged from 1.5 months to 2 years. Moreover, the age of the patients in these trials ranged from 25.1 to 63.5 years. The Body mass index (BMI) of patients ranged from 20.5 to 38.3 kg/m^2 and mean body weight ranged from 56.1 to 110.4 kg (Table 2). All the trials included were double-blinded (except one) and multi-centric. The primary outcome measure in these trials was the quantitative assessment of change in baseline body weight due to the use of prescribed drugs.

Drugs causing weight gain versus placebo

Four out of twenty trials reported drug-induced weight gain among study participants as shown in Table 3. The increase in weight ranged from + 3.5 to + 8.0 %. Trials of piogliatzone (for prevention of stroke or myocardial infarction in patients with insulin resistance), espindolol (for treatment and prevention of cancer-related cachexia), brexpiprazole (adjunct therapy in major depressive disorder), and retigabine (partial epilepsy) reported significant weight gain among patients. In all these trials, weight gain was observed as a secondary outcome except one trial on espindolol in which weight gain was reported as a primary outcome measure [10-13]. The use of pioglitazone was found to be associated with maximum weight gain as compared to placebo in these trials.

Drugs causing weight loss versus placebo

Fourteen out of twenty trials reported drug-induced weight loss. Weight loss in these trials ranged from 4.6 to 12 %. Drugs included in these trials were betahistine (to counteract olanzapine associated weight gain), naltreaxone ER/bupripion ER (weight management agent), bupropion SR (for reduction of weight and depressive symptoms), liraglutide (weight

management agent), topiramate (weight management), phentermine (weight management), duloxetine (pain management), zonisamide (weight management), metformin (prevention of olanzapine induced weight gain), and orlistat (weight management). In all these trials, weight loss was observed as a primary outcome measure except one trial on duloxetine in which weight loss was observed as a secondary outcome [14-27]. The use of naltrexone ER/buropion ER as combination was associated with maximum weight when compared to placebo. Other trials also reported insignificant weight loss with the use of betahistine, zonisamide (low dose), bupropion SR (low dose) and metformin (dose: 850 mg) when compared to placebo (Table 3) ($p > 0.05$).

Comparison of two drugs causing weight change

Two out of twenty trials compared two drugs for weight changes. Weight loss in both trials ranged from 1.6 to 6 %, while weight gain associated with a drug was 1.4 %. Drugs included in these trials were antidiabetic medications including linagliptin, glimepiride, liraglutide, and semaglutide. The change in body weight was considered as a secondary outcome in both trials; while weight change was a confirmatory

secondary endpoint in one trial and side effect of treatment in another trial [28,29]. Weight gain was associated with the use of glimepiride (+ 1.4 %), while weight loss was reported with semaglutide (- 6 %) followed by liraglutide (- 2 %) and linagliptin (- 1.6 %) (Table 3).

Meta-analysis

All the twenty studies in the review were subjected to the inclusion criteria of meta-analysis. However, only five studies [14,22,23,26,27], met the inclusion criteria which were further included in the quantitative synthesis. These results indicate that drugs in this category were able to reduce weight by - 1.33 (CI 95 % -3.35, 0.68) when compared to standard treatment, however, the heterogeneity was high (I^2 = 99 %) (Figure 2).

Considering the high heterogeneity, one study by Krempf *et al* [23], was removed from the analysis, keeping in view its effect size in comparison to other studies. Subsequently, heterogeneity (I^2) was reduced to 61 %. The final analysis suggested that the drugs can cause a reduction in body weight by - 0.53 (CI 95% - 1.01, - 0.04, *p* = 0.04) as compared to the standard treatment (Figure 3).

Table 1: Quality assessment of included trials

| References	Concealment of randomization	RCT stopped early	Patients blinded	HCP blinded	DC blinded	OA blinded	Selective outcome reporting
Barak *et al* [14]	✓	✗	✓	✓	✓	✓	✓
Kernan *et al* [10]	✓	✗	✓	✓	✓	✓	✗
Stewart Coats *et al* [11]	✓	✗	✓	✓	✓	✓	✓
Fujioka *et al* [15]	✓	✗	✓	✓	✓	✓	✓
Fujioka *et al* [18]	✓	✗	✓	✓	✓	✓	✓
Bray *et al* [19]	✓	✗	✓	✓	✓	✓	✓
Golay *et al* [21]	✓	✗	✓	✓	✓	✓	✓
Jain *et a.* [16]	✓	✗	✓	✓	✓	✓	✓
Rossner *et al* [22]	✓	✗	✓	✓	✓	✓	✓
Gadde *et al* [20]	✓	✗	✓	✓	✓	✓	✓
Gallwitz *et al* [28]	✓	✗	✓	✓	✓	✓	✗
Gadde *et al* [24]	✓	✗	✓	✓	✓	✓	✓
Anderson *et al* [17]	✓	✗	✓	✓	✓	✓	✓
Thase *et al* [12]	✓	✗	✓	✓	✓	✓	✗
Frakes *et al* [25]	✓	✗	✓	✓	✓	✓	✗
French *et al* [13]	✓	✗	✓	✓	✓	✓	✗
Krempf *et al* [23]	✓	✗	✓	✓	✓	✓	✓
Baptista *et al* [27]	✓	✗	✓	✓	✓	✓	✓
Wu *et al* [26]	✓	✗	✓	✓	✓	✓	✓
Capehorn *et al* [29]	✗	✗	✗	✗	✗	✗	✓

HCP: Healthcare Provider; DC: Data Collector; OA: Outcome Assessors

Table 2: Summary of study characteristics

Reference	Study duration	Sample size (n)			Demographics				Treatment
		Total	Control	Intervention	Age (years)	Gender (Female %)	Mean weight (Kg)	BMI (Kg/m²)	
Barak *et al* [14]	4 months	35	20	15	26.7	28.4	72.06	24	Prevention of antipsychotic induced weight gain
Kernan *et al* [10]	5 years	3876	1937	1939	63.5	34.5	N/A	30	Prevention of stroke and myocardial infarction
Stewart Coats *et al* [11]	4 months	87	31	56	56.8	33.3	N/A	20.5	Cachexia
Fujioka *et al* [15]	14 months	2073	763	1310	47.2	79	100.8	36.2	Obesity
Fujioka *et al* [15]	14 months	3731	1244	2487	45.1	78.4	106.2	38.3	Obesity
Bray *et al* [19]	6 months	380	75	305	46.5	85.2	103.7	37.38	Obesity
Golay *et al* [21]	6 months	89	45	44	41.5	91	98.35	36.5	Binge eating disorder
Jain *et al* [16]	6.5 months	422	209	213	45	91	97.15	35.8	Obesity and depressive symptoms
Rossner *et al* [22]	2 years	729	243	486	44.2	82.3	97.83	35.1	Obesity
Gadde *et al* [20]	14 months	2487	994	1493	51.1	70	103.1	36.6	Obesity
Gallwitz *et al* [28]	2 years	1551	776	775	59.8	39.5	86.5	30.3	Diabetes
Gadde *et al* [24]	1 year	225	74	151	43	59.6	110.4	37.6	Obesity
Anderson *et al* [17]	12 months	327	112	215	41.5	84.95	100.2	37	Obesity
Thase *et al* [12]	1.5 months	353	178	175	44.7	70.4	N/A	29.8	Major depressive disorder
Frakes *et al* [25]	2.5 months	524	260	264	61	57	N/A	31.6	Knee pain
French *et al* [13]	4.5 months	305	152	153	37.2	54.1	76.5	27.4	Partial epilepsy
Krempf *et al* [23]	18 months	696	350	346	41.5	86.4	97.3	36.1	Obesity
Baptista *et al* [27]	3.5 months	40	20	20	47.9	37.5	58.8	23.1	Prevention of olanzapine induced weight gain
Wu *et al* [26]	3 months	40	20	20	25.1	45.9	56.1	21.45	Prevention of olanzapine induced weight gain
Capehorn *et al* [29]	7.5 months	577	287	290	59.5	43.3	96.9	33.7	Diabetes
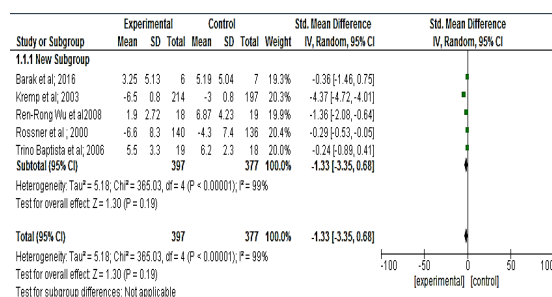
Figure 2: Impact of drug therapy on the weight loss of the patients (SD = standard deviation; IV = inverse variance)
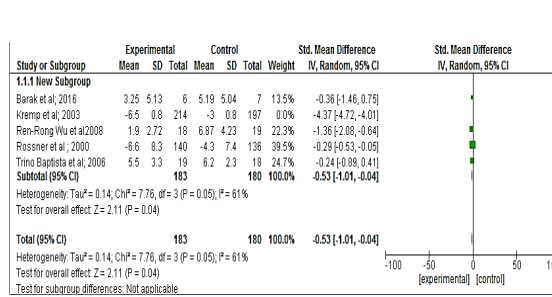
Figure 3: Impact of drug therapy on the weight loss of patients by excluding the study of Krempf *et al* [23] (SD = standard deviation; IV = inverse variance)

DISCUSSION

This quantitative and qualitative synthesis of randomized controlled trials suggests that the use of medication for chronic illnesses is substantially associated with weight changes. Various drugs may cause weight gain (espindolol, pioglitazone) [10-13], while others contribute to weight loss (betahistine, duloxetine, metformin) [14-29]. Since the weight changes may portend considerable risks of non-adherence and adverse outcomes among patients, there is a dire need to consider variation in weight change as an important outcome for consideration.

A total of four drugs were studied for weight gain against placebo. Maximum weight gain was associated with pioglitazone followed by retigabine and brexpiprazole, while espindolol caused the least weight gain [10-13]. It has been established that water retention with the use of pioglitazone causes weight gain.

Table 3: Summary of included studies evaluating the efficacy of drugs on body weight

Reference	Drug dose and frequency		Outcome (Change in weight)		
	Control	*Intervention*	*Control*	*Intervention*	*P value[1]*
Barak *et al* [14]	Placebo	Betahistine (48 mg/day)	+ 6.9 Kg	+ 5.6 Kg	0.197
Kernan *et al* [10]	Placebo	Pioglitazone (45mg/day)	-0.5 Kg	+2.6 Kg	<0.001
Stewart Coats *et al* [11]	Placebo	Espindolol (10mg b.d)	-0.21Kg/4weeks	+0.54 Kg/4weeks	< 0.0001
Fujioka *et al* [15]	Placebo	32mg Naltrexone ER/ 360mg Bupropion ER/day	N/A	-11.7%	< 0.001
Fujioka *et al* [18]	Placebo	Liraglutide (3.0mg/day)	N/A	- ≥ 5%	N/A
Bray *et al* [19]	Placebo	Topiramate (64mg/day)	- 3.6%	- 5.8% with 64mg/d - 6.5% with 96mg/d - 8.2% with 192mg/d - 8.5% with 384mg/d	< 0.05
Golay *et al* [21]	Placebo	Orlistat (120mg t.i.d)	- 2.3%	- 7.4%	0.0001
Jain *et al* [16]	Placebo	Bupropion SR (300mg/day)	- 1.8%	-4.6%	< 0.001
Rossner *et al* [22]	Placebo	Orlistat (120mg t.i.d)	- 6.6%	- 8.6% for 60mg t.i.d - 9.7% for 120mg t.i.d	0.005 < 0.001
Gadde *et al* [20]	Placebo	Phentermine 15.0mg plus Topiramate (92.0mg/day)	-5%	- ≥10%	<0·0001
Gallwitz *et al* [28]	Linagliptin 5mg/day	Glimepiride (4mg/day)	- 1.4 kg	+ 1.3 Kg	<0·0001
Gadde *et al* [24]	Placebo	Zonisamide 400mg or (200mg/day)	-4.0Kg (−3.7%)	−4.4 kg for 200 mg (−3.9%) −7.3 kg for 400 mg (−6.8%)	0.79 0.009
Anderson *et al* [17]	Placebo	Bupropion SR 300mg/day (400mg/day)	- 5%	- 7.2% for 300mg/day - 10.0% for 400mg/day	0.0468 < 0.0001
Thase *et al* [12]	Placebo	Brexpiprazole (2mg/day)	+ 3.1%	+ 8.0%	< 0.0001
Frakes *et al* [25]	Placebo	Duloxetine (60/120 mg/day)	+ 0.1kg	- 1.1 kg	< 0.001
French *et al* [13]	Placebo	Retigabine (1,200 mg/day)	+ 0.3 kg (0.4%)	+ 2.6 kg (3.5%)	< 0.001
Krempf *et al* [23]	Placebo	Orlistat (120mg t.i.d)	-3.0%	-6.5%	0.0005
Baptista *et al* [27]	Placebo	Metformin (850mg b.d 1700mg/day)	+ 6.3 kg	+5.5kg	0.4
Wu *et al* [26]	Placebo	Metformin (750 mg/day)	+1.90 kg	+6.87 kg	< 0.02
Capehorn *et al* [29]	Liraglutide 1.2mg/day	Semaglutide (1mg/week)	-1.9 kg	-5.8 kg	<0.0001

However, the mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation [30]. Mild weight gain is common due to an increase in subcutaneous adipose tissue. Nevertheless, approximately 75 % increase in body weight among patients with Type II diabetes mellitus receiving pioglitazone is primarily attributed to water retention. Pioglitazone stimulates plasma renin activity and increases sodium and water retention in healthy subjects, which might explain edema among patients with Type II diabetes treated with pioglitazone. The renal collecting duct is a major site for increased fluid reabsorption in response to pioglitazone. It also increases appetite and carbohydrate craving. Hence, pioglitazone increases total body water, thereby accounting for major weight gain among patients [31,32]. On the other hand, weight gain due espindolol is related to an increase in muscle mass (12.7 ± 0.9 %) in just 4 weeks. The anabolic and catabolic transforming agent (ACTA) such as espindolol increases muscle mass and decreases fat mass; thereby causing weight gain [33]. The mechanism of weight gains by brexpiprazole is multifactorial which involves various factors such as an increase in appetite, hormonal changes, slowed metabolism, and lower motivation to exercise [34]. Retigabine (ezogabine) therapy is associated with dose-related weight gain where increase in weight of 1.2, 1.6 and 2.7 Kg was observed with retigabine at doses of 600, 900 and 1200 mg respectively in one clinical trial [13,35].

A total of ten drugs were studied for weight loss against placebo. Maximum weight loss was observed with naltrexone ER/buripion ER combination treatment followed by liraglutide and phentermine plus topiramate [14-24,26,27] while the least weight loss was observed with the use of duloxetine [25].

The exact mechanism of betahistine-induced weight loss is not clear. Prior animal studies have suggested that betahistine suppresses food intake and reduces body weight, but there are sparse human data assessing the effects of betahistine on metabolism [36,37]. The mechanism by which the combination of naltrexone SR/bupropion SR induces weight loss is also debatable. The combination is hypothesized to work synergistically in the hypothalamus and the mesolimbic dopamine circuit to promote safety, reduce food intake, and enhance energy expenditure or may work as a lipase inhibitor to target appetite control mechanisms [38,39].

The exact mechanism of weight loss by liraglutide is also unknown. It is thought that liraglutide (glucagon-like peptide) exerts incretin effects and suppresses food intake in humans, and delays gastric emptying. However, its therapeutic use is limited in clinical practice due to its short half-life [40,41]. Topiramate causes weight loss by suppressing food intake and by increasing lipoprotein lipase activity. Weight loss is primarily caused by a reduction in fat mass [42]. Orlistat decreases the absorption of dietary triglycerides by inhibiting the intestinal lipases. Orlistat therapy is also associated with a greater decline in plasma low-density lipoprotein-cholesterol concentrations than that expected from weight loss alone [43]. The mechanism of action of weight loss by zonisamide has not been fully investigated. However, it seems to act primarily through blockage of voltage-sensitive sodium channels, although there is some evidence for other mechanisms including blockage of T-type calcium channels and as a GABA mediator [44]. Duloxetine-treated patients experienced weight loss after short-term treatment, followed by modest weight gain with longer-term treatment suggesting that duloxetine has minimal effects on weight for the majority of patients. However, the basic mechanism through which duloxetine impacts body weight is unknown [45].

Metformin produces durable weight loss, and decreased food intake is considered a causative factor of weight loss. Other potential mechanisms include changes in insulin and leptin sensitivity, and regulation of fat oxidation [46]. The weight gain mechanism during the treatment with glimepiride is often multifactorial: less energy lost in the urine due to better blood sugar control and possible increased snacking due to low levels of blood sugar. In addition, the drug appears to increase fat storage for a not yet well-understood reason [47]. The mechanism of action of semaglutide induced weight loss included low energy intake, decrease in appetite, control on eating preferences, fewer food cravings, and reduction of body fat mass [48]. However, the exact mechanism by which linagliptin causes weight change is not known.

Limitations of the study

The findings of the review should be considered in light of few limitations. This review is limited to only those drugs which were used for the management of chronic conditions and reported in the literature consistently. Since other prescribed drugs may also affect body weight, the findings of the current review do not exclude the association of other drugs with weight

changes. Moreover, it would be difficult to generalize the results as study population, doses of drugs, treatment duration and dietary interventions widely vary across included studies.

CONCLUSION

This review presents comparative evidence of weight change by commonly prescribed drugs. Pioglitzone, brexpiprazole, espindolol, ezogabine and glimepiride cause weight gain while naltrexone, bupropion, betahistine, topiramate, phentermine, zonisamide, semaglutide, linagliptin, liraglutide, orlistat, duloxetine and metformin are associated with weight loss. In clinical trials, both height and weight are recorded on routine basis but reported rarely. Future studies should report the incidence of weight change with sufficient details and longer durations of follow-up. This review will serve as a guidance for choosing the most appropriate drug for an effective regimen when multiple drugs are available. Selection of appropriate drugs, monitoring of body weight, regular exercise, and dietary interventions will result in an optimized clinical outcome. Patients must be provided with specific information regarding drugs having potential for weight change before initiation of treatment. This will ensure the management of body weight and also improve medication adherence.

DECLARATIONS

Acknowledgement

Conflict of interest

No conflict of interest is associated with this work

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Iram Ijaz, Yusra Habib Khan and Tauqeer Hussain Mallhi conceptualized the study plan. Amna Javed, Umda-tun-Nisa Saleem, Abdulaziz Ibrahim Alzarea, Abdullah Salah Alanazi and Nasser Hadal Alotaibi did literature search, screening, data extraction and drafted the manuscript. Raja Ahsan Aftab, Muhammad Hammad Butt and Muhammad Salman performed meta-analysis. Yusra Habib Khan and Tauqeer Hussain Mallhi

assisted in interpreting the results. Yusra Habib Khan, Tauqeer Hussain Mallhi, Raja Ahsan Aftab, Muhammad Hammad Butt, Muhammad Salman and Nasser Hadal Alotaibi assessed the data quality and approved the final version of manuscript for submission. All authors have critically reviewed the manuscript and agreed with the current version of the manuscript.

Open Access

REFERENCES

1. Barness LA, Opitz JM, Gilbert-Barness E. Obesity: genetic, molecular, and environmental aspects. Am J Med Genet A 2007; 143(24): 3016 –3034.
2. Obesity and overweight. (n.d.). Retrieved February 1, 2021, from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
3. Products Data Briefs Number 360 February 2020. (Accessed June 26, 2020). https://www.cdc.gov/nchs/products/databriefs/db360.htm
4. Vasan RS, Pencina MJ, Cobain M, Freiberg MS, D'Agostino RB. Estimated risks for developing obesity in the Framingham Heart Study. Ann Intern Med 2005; 143(7): 473– 480.
5. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA 2007; 298(17): 2028 – 2037.
6. Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900000 adults: collaborative analyses of 57 prospective studies. Lancet 2009; 373(9669): 1083–1096.
7. Preston SH, Stokes A. Contribution of obesity to international differences in life expectancy. Am J Public Health 2011; 101(11): 2137– 2143.
8. National Audit Office. Tackling Obesity in England. London, The Stationery Office Ltd, 2001.
9. Walker A. The cost of doing nothing—the economics of obesity in Scotland. Robertson Centre for Biostatistics, University of Glasgow, 2003.
10. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, Guarino PD, Lovejoy AM, Peduzzi PN, Conwit R. Pioglitazone after ischemic stroke or transient

ischemic attack. *N Engl J Med* 2016; 374(14): 1321-1331.

11. Stewart Coats AJ, Ho GF, Prabhash K, von Haehling S, Tilson J, Brown R, Beadle J, Anker SD. Espindolol for the treatment and prevention of cachexia in patients with stage III/IV non-small cell lung cancer or colorectal cancer: a randomized, double-blind, placebo-controlled, international multicentre phase II study (the ACT-ONE trial). *J Cachexia Sarcopenia Muscle* 2016; 7(3): 355-365.

12. Thase ME, Youakim JM, Skuban A, Hobart M, Augustine C, Zhang P, McQuade RD, Carson WH, Nyilas M, Sanchez R, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. *J Clin Psychiatry Ment Health* 2015; 76(9): 1224-1231.

13. French JA, Abou-Khalil BW, Leroy RF, Yacubian EMT, Shin P, Hall S, Mansbach H, Nohria V. Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy. *Neurol* 2011; 76(18): 1555-1563.

14. Barak N, Beck Y, Albeck JH. A randomized, double-blind, placebo-controlled pilot study of betahistine to counteract olanzapine-associated weight gain. *J Clin Psychopharmacol* 2016; 36(3): 253-256.

15. Fujioka K, Plodkowski R, O'neil PM, Gilder K, Walsh B, Greenway FL. The relationship between early weight loss and weight loss at 1 year with naltrexone ER/bupropion ER combination therapy. *Int J Obes* 2016; 40(9): 1369-1375.

16. Jain AK, Kaplan RA, Gadde KM, Wadden TA, Allison DB, Brewer ER, Leadbetter RA, Richard N, Haight B, Jamerson BD, et al. Bupropion SR vs. placebo for weight loss in obese patients with depressive symptoms. *Obes Res* 2002; 10(10): 1049-1056.

17. Anderson JW, Greenway FL, Fujioka K, Gadde KM, McKenney J, O'neil PM. Bupropion SR enhances weight loss: a 48-week double-blind, placebo-controlled trial. *Obes Res* 2002; 10(7): 633-641.

18. Fujioka K, O'Neil PM, Davies M, Greenway F, Lau DCW, Claudius B, Skjøth TV, Jensen CB, Wilding JPH. Early weight loss with liraglutide 3.0 mg predicts 1-year weight loss and is associated with improvements in clinical markers. *Obesity* 2016; 24(11): 2278-2288.

19. Bray GA, Hollander P, Klein S, Kushner R, Levy B, Fitchet M, Perry BH. A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. *Obes Res* 2003; 11(6): 722-733.

20. Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, Day WW. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomized, placebo-controlled, phase 3 trial. *Lancet* 2011; 377(9774): 1341-1352.

21. Golay A, Laurent-Jaccard A, Habicht F, Gachoud JP, Chabloz M, Kammer A, Schutz Y. Effect of orlistat in

obese patients with binge eating disorder. *Obes Res* 2005; 13(10): 1701-1708.

22. Rössner S, Sjöström L, Noack R, Meinders AE, Noseda G. European Orlistat Obesity Study. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. *Obes Res* 2000; 8(1); 49-61.

23. Krempf M, Louvet JP, Allanic H, Miloradovich T, Joubert JM, Attali JR. Weight reduction and long-term maintenance after 18 months treatment with orlistat for obesity. *Int J Obes* 2003; 27(5); 591-597.

24. Gadde KM, Kopping MF, Wagner HR, Yonish GM, Allison DB, Bray GA. Zonisamide for weight reduction in obese adults: a 1-year randomized controlled trial. *Arch Intern Med* 2012; 172(20): 1557-1564.

25. Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. *Curr Med Res Opin* 2011; 27(12): 2361-2372.

26. Wu RR, Zhao JP, Guo XF, He YQ, Fang MS, Guo WB, Chen JD, Li LH. Metformin addition attenuates olanzapine-induced weight gain in drug-naive first-episode schizophrenia patients: a double-blind, placebo-controlled study. *Am J Psychiat* 2008; 165(3): 352-358.

27. Baptista T, Martínez J, Lacruz A, Rangel N, Beaulieu S, Serrano A, Arapé Y, Martinez M, de Mendoza S, Teneud L et al. Metformin for prevention of weight gain and insulin resistance with olanzapine: a double-blind placebo-controlled trial. *Can J Psychiat* 2006; 51(3): 192-196.

28. Gallwitz B, Rosenstock J, Rauch T, Bhattacharya S, Patel S, von Eynatten M, Dugi KA, Woerle H-J. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. *Lancet* 2012; 380(9840): 475-483.

29. Capehorn MS, Catarig AM, Furberg JK, Janez A, Price HC, Tadayon S, Vergès B, Marre M. Efficacy and safety of once-weekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab* 2020; 46(2): 100-109.

30. Water retention with pioglitazone causes weight gain. (2006, March 28). *Diabetes in control. A free weekly diabetes newsletter for medical professionals.*

31. Basu A, Jensen MD, McCann F, Mukhopadhyay D, Joyner MJ, Rizza RA. Effects of pioglitazone versus glipizide on body fat distribution, body water content, and hemodynamics in type 2 diabetes. *Diabetes Care* 2006; 29(3): 510-514.

32. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. *The*

Pioglitazone 001 Study Group. Diabetes care 2000; 23(11): 1605-1611.

33. *Pötsch MS, Tschirner A, Palus S, von Haehling S, Doehner W, Beadle J, Coats AJ, Anker SD, Springer J. The anabolic catabolic transforming agent (ACTA) espindolol increases muscle mass and decreases fat mass in old rats. J Cachexia Sarcopenia Muscle 2014; 5(2): 149-158.*

34. *Kane JM, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, Nyilas M, Carson WH, Sanchez R, Eriksson H. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Schizophr Res 2015; 164(1-3): 127-135.*

35. *McMillin GA, Krasowski MD. Therapeutic drug monitoring of newer antiepileptic drugs. In: Clinical Challenges in Therapeutic Drug Monitoring. Elsevier 2016; pp 101-134.*

36. *Deng C, Lian J, Pai N, Huang XF. Reducing olanzapine-induced weight gain side effect by using betahistine: a study in the rat model. J Psychopharmaco 2012; 26(9): 1271-1279.*

37. *Barak N, Greenway FL, Fujioka K, Aronne LJ, Kushner RF. Effect of histaminergic manipulation on weight in obese adults: a randomized placebo-controlled trial. Int J Obes 2008; 32(10): 1559-1565.*

38. *Billes SK, Greenway FL. Combination therapy with naltrexone and bupropion for obesity. Expert Opin Pharmacother 2011; 12(11): 1813-1826.*

39. *Greenway FL, Whitehouse M, Guttadauria M, Anderson JW, Atkinson RL, Fujioka K, Gadde KM, Gupta AK, O'neil P, Schumacher D, et al. Rational design of a combination medication for the treatment of obesity. Obesity 2009; 17(1): 30-39.*

40. *Harder H, Nielsen L, Thi TD, Astrup A. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. Diabetes Care 2004; 27(8): 1915-1921.*

41. *Ladenheim EE. Liraglutide and obesity: a review of the data so far. Drug Des Devel Ther 2015; 9: 1867-1875.*

42. *Antel J, Hebebrand J. Weight-reducing side effects of the antiepileptic agents topiramate and zonisamide. Appetite control 2012; 433-466.*

43. *Mittendorfer B, Ostlund Jr RE, Patterson BW, Klein S. Orlistat inhibits dietary cholesterol absorption. Obes Res 2001; 9(10): 599-604.*

44. *Kyllerman M, Ben-Menachem E. Zonisamide for progressive myoclonus epilepsy: long-term observations in seven patients. Epilepsy Res 1998; 29(2): 109-114.*

45. *Wise TN, Perahia DG, Pangallo BA, Losin WG, Wiltse CG. Effects of the antidepressant duloxetine on body weight: analyses of 10 clinical studies. Prim Care Companion J Clin Psychiatry 2006; 8(5): 269-278.*

46. *Malin SK, Kashyap SR. Effects of metformin on weight loss: potential mechanisms. Curr Opin Endocrinol Diabetes Obes 2014; 21(5): 323-329.*

47. *McCall AL. Clinical review of glimepiride. Expert Opin Pharmacother 2001; 2(4): 699-713.*

48. *Blundell J, Finlayson G, Axelsen M, Flint A, Gibbons C, Kvist T, Hjerpsted JB. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab 2017; 19(9): 1242-1251.*