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Review

Weight-centric treatment of depression and chronic pain

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ABSTRACT

Background: Depression and chronic pain are two major chronic non-communicable diseases (CNCD). Considering the bidirectional relationship between obesity and CNCD, it is of the utmost importance to understand the effect of medications utilized to treat these diseases on body weight.
Methods: This is a clinical review on the effect of medications for depression and chronic pain on body weight. We searched PubMed, Scopus, MEDLINE, and Google Scholar databases for studies on the topic from January 1, 1950 to April 1, 2022 in English language. Additionally, we present expert opinions in the fields of obesity, depression and chronic pain, providing a weight-centric approach to treat depression and chronic pain.
Results: Several antidepressant and chronic pain medications are associated with weight gain. Selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidases, mirtazapine and trazodone are common antidepressants that can increase body weight while bupropion is significantly associated with weight loss. Gabapentin and pregabalin are common chronic pain medications that are linked to weight gain. On the other hand, topiramate is associated with significant weight loss. Obesity, depression and chronic pain experts recommend avoiding medications that can increase body weight if another effective alternative is available.
Conclusion: By shifting prescribing practices toward a weight-conscious approach (i.e., switching from weight gain medications to weight loss/neutral), it is possible to mitigate the incidence of drug-induced weight gain.

1. Introduction

Chronic non-communicable diseases (CNCD) incorporate a wide range of conditions including obesity, diabetes, cardiovascular and respiratory diseases, cancers, and mental-health problems. CNCD are a major cause of mortality in which they account for more than 50% of global deaths [1]. Several studies have shown that obesity is one of the most important and modifiable risk factors for CNCD [2–4]. In fact, treating obesity (e.g., preventive nutrition) has a key role in the regression and prevention of CNCD [5].

Overweight and obesity stem from an energy imbalance, when caloric intake exceeds expenditure [6]. Although the causes and pathophysiology of obesity and overweight are complex (e.g., slow metabolism [7]), they are mainly driven by sub-optimal dietary and exercise patterns [8]. As a result of the multiple comorbidities related to obesity, it ranks among the leading causes of preventable deaths in the United States [9]. Considering the high prevalence of overweight and obesity worldwide [10] and the associated medical [11] and financial burdens [12], targeting the modifiable causes of weight gain is of extreme importance.

The relationship between obesity and most CNCD is bidirectional [13]. Obesity is a CNDC as well as contributes to the development of other CNCD (e.g., depression, osteoarthritis), while these CNCD may also worsen or contribute directly to weight gain and obesity [14,15]. For example, weight-bearing osteoarthritis is a consequence of obesity [16], and the decreased mobility secondary to osteoarthritis may contribute to further worsening of obesity [16]. Furthermore, in certain instances, the treatment of CNCD (e.g., medications) may result in further weight gain [17,18]. Thus, the treatment for the CNCD can worsen obesity, which in

Abbreviations: CNCD, Chronic non-communicable diseases; SSRIs, Selective Serotonin Reuptake Inhibitors; SNRIs, Serotonin-Norepinephrine Reuptake Inhibitors; TCAs, Tricyclic Antidepressants; MAOIs, Monoamine Oxidase Inhibitors; NSAIDs, Nonsteroidal Anti-inflammatory Drugs; RCT, Randomized Clinical Trial.

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itself aggravates the CNCD, and the vicious cycle of obesity-related CNCD endures. For instance, the treatment of weight-bearing osteoarthritis with gabapentin may improve pain related to osteoarthritis; however, the most common side effect is weight gain and increased appetite [19]. Thus, the solution aggravated the root cause of the problem.

Discussing the side effect profile of a medication with patients is a critical feature in the prescription process [20]. Intolerable side effects are a primary reason for premature discontinuation or nonadherence to certain medications [21,22]. This may lead to deterioration of a medical or psychiatric condition [23], increased medication-related hospital admissions [24,25], increased financial burden to healthcare utilization [26], and worsened long-term outcomes including death [27]. Considering the high prevalence of CNCD such as depression [28] and chronic pain [29] in the general population and in patients with overweight and obesity [15,30], it is extremely significant to understand the effect of these diseases' medications on body weight. A more conscientious prescribing practice can result in improved and individualized care for patients on medical [31,32], psychological [33] and financial levels [31,32].

In this review series, we will discuss some common CNCD that may benefit from a weight-centric approach. We will describe the effect of the medications commonly prescribed for CNCD on body weight, and present an expert opinion on the weight centric approach for treating CNCD. We will start this series with two prevalent diseases: depression and chronic pain.

2. Methods

The present paper is a clinical review based on publications focused on the effect of medications for depression and chronic pain on body weight. We searched PubMed, Scopus, MEDLINE, and Google Scholar databases for studies on the topic from January 1, 1950 to April 1, 2022 in English. In particular, we considered data from systematic reviews, meta-analyses, randomized clinical trials (RCTs), and prospective and retrospective cohort studies to assess the association between depression and chronic pain medications with body weight. Additionally, we present expert opinions in the fields of obesity, depression and chronic pain. They provided a weight-centric approach to treat depression and chronic pain.

3. Results

3.1. Depression

Major depressive disorder is a heterogenous condition that has various presentations and is associated with a broad constellation of symptoms. The diagnosis requires fulfilling five or more symptoms (e.g., depressed mood, anhedonia, weight loss/gain or appetite change, insomnia/hypersomnia, psychomotor agitation, fatigue, feeling of worthlessness or inappropriate guilt, diminished concentration ability, and suicidal thoughts) over a period of 2 weeks [34].

Depressive disorders are considered to be among the most common causes of disability worldwide [35]. In the United States, the estimated lifetime risk of a major depressive episode is around 30% [36]. Moreover, in the last two decades approximately 800,000 deaths were attributed to suicide in the United States [37]. Hence, considering the high rates of morbidity and mortality associated with depression, there is a great need to provide a reliable treatment for this serious disease.

The treatment of depression primarily focuses on two treatment interventions: psychotherapy and pharmacotherapy [38]. Psychotherapy is an important first line treatment of depression. This includes cognitive behavioral therapy (1st line) [39], interpersonal psychotherapy [40] and problem-solving therapy [41]. Antidepressants are recommended if the patient reports no improvement with psychotherapy, if the patient is not suitable for any type of psychotherapy, or if a patient meets criteria for moderate to severe depression [38]. First-line pharmacotherapies include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants (i.e., mirtazapine and bupropion) [38,42–44]. Second-line pharmacotherapies include combining the initial antidepressant with a second one, or augmenting with a non-antidepressant (e.g., a mood stabilizer) [45]. Older agents such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are considered 3rd and 4th line respectively due to their side effects and safety profiles [46]. Due to their similar efficacy, the choice of these drugs depends on several factors including side effects, drug interaction, cost, and comorbid medical conditions [38].

While multifactorial in etiology, depression and obesity share, in part, common biological and behavioral mechanisms including genetics, epigenetics, ethnic background, insulin resistance, inflammation, unhealthy lifestyles, and other environmental influences [47,48]. In fact, the roles of genetics and epigenetics (i.e., genetic predisposition) have been shown to be highly associated with the development of obesity [49] and depression [50]. Atypical depressive symptoms (i.e., carbohydrate craving, hypersomnia), binge eating behavior, and antidepressant drug side effects all contribute to obesity [51]. Several studies show a reciprocal link between depression and obesity. Depression is considered to be a predictive factor for the development of obesity [15]. The dysregulated stress systems [52] and unhealthy lifestyles [53] of individuals with depression are possible mechanisms behind the increased prevalence of obesity in patients with depression. In addition, obesity can also increase the risk of depression [15]. A possible explanation is the negative effects of obesity on self-image and somatic consequences [15]. In fact, several studies have also shown that weight loss can improve depressive symptoms in patients with obesity [54,55]. Hence, there is a clear bidirectional association between obesity and depression. Based on this association discussed by Freshwater et al. [13], we will present a weight-centric approach to treat depression.

3.1.1. Antidepressants: Effect on Body Weight

3.1.1.1. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). SSRIs and SNRIs are two classes of antidepressant medications that inhibit serotonin and serotonin-norepinephrine reuptake at the level of the brain, respectively [56,57]. In 1984, Wurtman et al. showed the role of serotonin in reducing carbohydrate intake which attributed an anorexic role to serotonergic drugs (i.e., SSRIs and SNRIs) [58]. Subsequent studies showed that the activation of hypothalamic serotonin receptors reduce the intake of dietary protein and fat rather than that of carbohydrates [59]. However, multiple rodent and human studies show that long-term use of SSRIs and SNRIs is associated with weight gain [60].

In a systematic review done between 2008 and 2019, most of the included cohort studies showed a 5% weight gain after the use of antidepressants [61]. However, the effect of each SSRI and SNRI on body weight differs due to variable degrees of action on the serotonergic, noradrenergic, dopaminergic, and histaminergic systems [61,62]. In another comprehensive review and meta-analysis, citalopram, sertraline, and escitalopram had no significant effect on body weight while paroxetine had the greatest long-term increase in body weight [62]. Although fluoxetine showed anorexigenic effects in the short term, restoration of this effect [62] or even weight gain [63] occurred during the maintenance period. Similarly, SNRIs were associated with a slight decrease in weight in the short term, followed by an increase over the long term [62,64–66]. In another population-based cohort study over 10 years, SSRIs seemed to be associated with weight gain (RR 1.21; 95% CI [1.20–1.23]): escitalopram (RR 1.21; 95%CI [1.20–1.23]), citalopram (RR 1.26; 95% CI [1.23–1.28]), fluoxetine (RR 1.21; 95% CI [1.18–1.24]), sertraline (RR 1.20; 95% CI [1.16–1.24]), and paroxetine (RR 1.05; 95% CI [1.00–1.10]) [67]. SNRIs were also associated with an increase in body weight (RR 1.17; 95% CI [1.13–1.21]): duloxetine (RR 1.23; 95% CI [1.15–1.31]) and venlafaxine (RR 1.15; 95% CI [1.10–1.20]) [67].

3.1.1.2. Tricyclic antidepressants (TCAs). TCAs are a group of antidepressant medications that block the reuptake of serotonin and

Table 1
The effect of different medications for depression on body weight.

Depression					
Medication Group	Medication	Weight Gain	Weight Neutral	Weight Loss	Reference
SSRIs	Fluoxetine	X*	X*	X**	[62,63]
	Citalopram, sertraline, escitalopram	X	X		[55]
	Paroxetine	X			[55]
SNRIs	All	X			[62,64]
TCAs	All	X	X		[68]
MAOIs	All	X			[74]
Atypical Antidepressants	Mirtazapine	XX			[64,77]
	Trazodone	X	X		[78]
	Bupropion			XX	[100]
	Vortioxetine		X		[91]

Title: The effect of different medications for depression on body weight.
X: <5% of total body weight change; XX: ≥5% of total body weight change; *: Long-term (>4 months); **:Short-term (4–12 weeks).
SSRIs: Selective Serotonin Reuptake Inhibitors; SNRIs: Serotonin-Norepinephrine Reuptake Inhibitors; TCAs: Tricyclic Antidepressants; MAOIs: Monoamine Oxidase Inhibitors.

norepinephrine [68]. They are known to be associated with weight gain due to their high affinity to H1 receptors [66,69]. Berken et al. reported a linear weight gain of 0.59–1.32 kg/month which was the main reason behind the discontinuation of TCA in a cohort of patients [70]. In addition, Gafoor et al. reported in their cohort study that TCA use was associated with weight gain (RR 1.21; 95% CI [1.19–1.23]): dosulepin (RR 1.09; 95% CI [1.03–1.15]), amitriptyline (RR 1.17; 95% CI [1.15–1.19]), and nortriptyline (RR 1.16; 95% CI [1.14–1.18]) [67]. On the other hand, other studies conducted over 1, 4.4, and 18 years showed that there was no significant weight gain associated with TCAs [60,71,72].

3.1.1.3. Monoamine oxidase inhibitors (MAOIs). MAOIs are another class of antidepressants that inhibit monoamine oxidation [73]. MAOIs can result in weight gain through their effect on appetite control. One possible mechanism is through reducing the blood glucose which creates hunger-stimulating effects, increasing the food/caloric intake [74,75]. In a study by Rabkin et al., patients taking phenelzine or tranylcypromine had a significant weight gain in addition to other associated side effects such as sexual dysfunction which together culminated in the discontinuation of the drug [76]. Other studies show that phenelzine is the MAOI that is most likely to induce weight gain [74].

3.1.1.4. Atypical antidepressants (mirtazapine, trazodone, bupropion and vortioxetine). Mirtazapine and trazodone are two atypical antidepressants that work on the serotonergic system [77,78]. Compared to all other antidepressants, mirtazapine seems to be associated with the highest incidence of weight gain (RR 1.5; 95% CI [1.45–1.56]) [67]. Although less associated with weight gain, trazodone is also linked to increase in body weight (RR 1.19; 95% CI [1.11–1.28]) [67]. However, other studies on trazodone vary between showing weight gain or weight neutral effects during the follow-up period [79].

Bupropion is a norepinephrine and dopamine reuptake inhibitor that is currently prescribed for depression and smoking cessation [80]. The mechanism of action behind this drug is poorly understood but it is theorized that the synergism of these two drugs act on the hypothalamus and mesolimbic dopamine pathway to promote fullness, reduce food intake [81] and enhance energy expenditure [82,83]. In a 2019 meta-analysis, bupropion was shown to be associated with weight loss [61]. In another 24-week multicenter, double-blinded, placebo-controlled study, bupropion was significantly associated with weight loss in a dose-dependent manner (Bupropion SR 300: 7.2% weight loss; Bupropion SR 400: 10.1% weight loss) [84]. Bupropion is a component of a Food and Drug Administration (FDA) approved weight loss medication in combination to naltrexone (Contrave) [85]. After demonstrating a safe profile, Contrave was approved by the FDA in September 2014 [82]. The weight loss associated with Contrave ranged between 5.9% and 11.5% at 56 weeks in the Contrave Obesity Research Clinical Trials (4,536 patients) [86–89]. The most common side effects reported with Contrave are nausea/vomiting, constipation/diarrhea, headache, dizziness, insomnia, and dry mouth [82].

Vortioxetine is another atypical antidepressant that modulates and stimulates serotonergic transmission [90]. In a systematic review, vortioxetine had no significant effect on body weight [91]. In another multi-center, open-label, 52-week extension study on 836 patients, there were no clinically meaningful weight changes reported among the groups administered different doses of vortioxetine (i.e., 2.5, 5, or 10 mg/day) [92].

3.1.1.5. Antipsychotics. Antipsychotics have been FDA approved as adjunctive treatment to antidepressants for depression. These medications include quetiapine, aripiprazole, brexpiprazole and olanzapine [93]. Most antipsychotics, particularly olanzapine and quetiapine, have been associated with weight gain [94]. In fact, weight increases rapidly during the initial phase after initiating these antipsychotics and continues in the long term [94]. The effect of each antipsychotic on body weight will be discussed in a future review on the weight-centric treatment of psychiatric disorders.

3.1.2. Expert Opinion: Weight-centric Approach

The choice of antidepressants depends highly on their side effect profile. Apart from body weight concerns, the medications used to treat depression have various side effects that tailor their management. For example, SSRI and SNRIs are associated with sexual dysfunction [95], SNRI with hypertension [96], and mirtazapine with hypersomnia [97]. Hence, the selection of antidepressants must be a critical and individualized process that is unique to each patient.

3.1.2.1. Weight-centric management. In patients with obesity or patients concerned about possible weight gain, reviewing and considering equally efficacious treatment options with less weight liability has great clinical merit. For patients who have responded to antidepressant treatment, but have a higher risk-benefit ratio, by virtue of weight gain, clinical options need to be reviewed. This would include discontinuing effective but intolerable antidepressants, which has risk for mood relapse, adding a medication that could possibly mitigate weight gain, or consider an alternative, less weight-liable antidepressant which may not have same degree of mood improvement as the former treatment that was discontinued. In fact, in certain instances when antidepressants with weight gain profile are prescribed, it is of crucial importance to explain the effect of these medications on body weight to the patient. When appropriate counselling is provided, patients may counteract this weight gain effect with modification to their food intake or energy expenditure. For example, patients may want to decrease their calorie intake or increase their exercise activity to prevent or mitigate the increase in body weight.

In addition, in patients with overweight/obesity, another antiobesity medication (AOM) (e.g., liraglutide, semaglutide) might be needed. The addition of an AOM will depend on the eligibility of patients (body-mass index [BMI] > 27 kg/m^2 with other comorbidities or BMI > 30 kg/m^2), and the need for such medication based on the patients' characteristics (i.e., physical activity, age, and weight). Older patients who are physically inactive and have obesity might need to incorporate an AOM within their treatment plan. Hence, this process should be tailored to each individual.

A systematic review and meta-analysis on the effect of intentional weight loss on depression showed that patients with obesity experienced a reduction in symptoms of depression after weight loss trials [98]. In another systematic review, the comorbidity between both obesity and depression resulted in a bad prognosis [18]. On the other hand, patients who are underweight can be suitable candidates for medications associated with weight gain (e.g., mirtazapine). For example, patients with advanced stages of cancer presenting with cachexia and insomnia can benefit from mirtazapine to gain weight and improve their sleep cycle [99]. In short, the decision of medication use must be based on the whole picture of side effects in which weight change is a major component (Table 1).

3.2. Chronic pain

According to the International Association for the Study of Pain (IASP), chronic pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage [101]. Chronic pain presents with a wide spectrum of symptoms ranging from headache, back and neck pain, to any pain that persists beyond normal tissue healing time (i.e., around 3 months) [102]. In addition, pain can be categorized into two main groups: nociceptive and neuropathic. Nociceptive pain is associated with actual or potential tissue damage that results in an activity in neural pathways (e.g., pain after surgery, arthritis, sport-injury). On the other hand, neuropathic pain may present without any demonstrable physical finding due to excess stimulation of nociceptor pathways. This type of pain is initiated by lesions in the nervous system and maintained via several mechanisms including damaging the inhibitory pathways of pain sensation [103].

The prevalence of chronic pain ranges between 11% and 40% [104] and the annual incidence is estimated to be around 8% [105]. The Institute of Medicine reported that one in three Americans complain of chronic pain, affecting 116 million adults which is greater than the total of diabetes, heart disease and cancer combined [106,107]. In addition to its high prevalence, chronic pain is a highly debilitating condition with substantial financial burden. In 2008, the Medical Expenditure Panel Survey showed that the annual costs associated with chronic pain ranged between 560 and 635 billion dollars [108].

The key to achieving an effective relief of pain relies on basing the management on a comprehensive, multifactorial and personalized treatment [109]. Non-pharmacological treatments include physical rehabilitation programs and behavioral management in a bio-psychosocial approach to pain management [110]. Pharmacotherapy choice depends on the type of pain. Neuropathic pain is usually treated with first-line treatments including TCAs, SNRIs, gabapentin, or pregabalin [111]. Carbamazepine is a first line choice for idiopathic trigeminal neuralgia [112]. In addition, inflammatory and mechanical/compressive pain are managed with NSAIDs or paracetamol [113].

In several studies, obesity was associated with persistent pain complaints [114]. For example, in a cohort of 6,796 patients, 2.9% with normal BMI, 7.7% with BMI 31–35 kg/m^2, and 11.6% with BMI of 36 kg/m^2 reported low back pain ($p < 0.05$) [115]. Increased loading on the joints and spine can cause defective changes in cartilages [116] and structure damage of the back [117] which can lead to chronic pain. Moreover, increased weight results in abnormal posture and gait patterns which may result in altered knee and ankle mechanics in ambulation, resulting in increased sensation of pain [118,119]. Other mechanisms including disturbed sleep [119,120], altered levels of hormones (e.g., leptin and ghrelin) [121] and sedentary lifestyle [122] may play a role in the relationship between obesity and chronic pain. In addition, chronic pain (e.g., osteoarthritis) can also be a risk factor for gaining weight and developing obesity [16]. Hence, these conditions are interrelated and the treatment of one disease can be dependent on the other.

3.2.1. Pain Relievers: Effect on Body Weight

3.2.1.1. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Acetaminophen and NSAIDs are two classes of analgesic medications that inhibit the cyclooxygenase (COX) pathways [123–125]. To our knowledge, an association between acetaminophen and weight gain has not been documented. Since obesity is associated with inflammation [126], Boaz et al. hypothesized that anti-inflammatory drugs (e.g., aspirin) can cause weight loss [127]. In their retrospective study on 202 patients with type-2 diabetes, exposure to anti-inflammatory drugs increased the odds of weight loss by 2.3 times ($p = 0.02$) [127]. More trials are needed to explain this association.

3.2.1.2. Antidepressants: TCAs and SNRIs. Antidepressants including TCAs and SNRIs play a major role in relieving chronic pain [128]. Their effect on body weight is discussed in the "Depression" section of this review.

3.2.1.3. Anticonvulsant. Some anticonvulsants have shown to be effective in treating chronic neuropathic pain [129,130]. There is evidence that these medications can cause weight gain, though the mechanism behind weight gain is not fully understood and can vary between drugs [131,132]. There are several proposed mechanisms that attempt to explain this association. First, these medications can work centrally affecting appetite regulation or peripherally causing drug-induced lowering of blood glucose level and increasing insulin levels [133]. Second, the antidiuretic role of anticonvulsants can cause edema reflecting a weight gain [134]. Third, altering the GABAergic inhibitory neurotransmission and the resulting sedation effect can alter energy expenditure which reflects an increase in body weight [133].

3.2.1.3.1. Gabapentin. Gabapentin is an anticonvulsant drug that can be used for neuropathic pain and fibromyalgia [135]. In a systematic review and meta-analysis, gabapentin was shown to be associated with a weight gain of 2.2 kg in 1.5 months [136]. In an open-label study, 57% and 23% of patients with seizures on gabapentin gained ≥5% and ≥10% of their baseline weight, respectively [19,137]. In another RCT in patients with postherpetic neuralgia, statistically significant weight gain was reported only in the high dose groups (2400 mg and 3600 mg) with a weight gain of 1.2 kg and 1.8 kg over 14 weeks, respectively ($p = 0.02$ and $p < 0.001$) [138].

3.2.1.3.2. Pregabalin. Pregabalin is another anticonvulsant drug that is effective in treating chronic neuropathic pain [139]. In patients with neuropathic pain, Siddall et al. reported in their multicenter RCT that more patients in the pregabalin group had a weight gain of 7% compared to the placebo group (11.4% vs 3.1%) [140]. In another RCT, pregabalin was associated with a dose-dependent weight gain [141]. Similarly, Beydoun et al. showed that the use of pregabalin in patients with partial seizures was associated with weight gain [142].

3.2.1.3.3. Carbamazepine. Carbamazepine is an anti-epileptic drug that decreases the synaptic transmission by modulating the voltage-gated sodium channels [143]. Gaspari et al. demonstrated in their study that carbamazepine is associated with weight gain in which 67% of patients on carbamazepine monotherapy reported a 2.35% increase in weight in six to eight months [144]. In an umbrella review published in 2018, Grootens et al. concluded that carbamazepine has a low risk of weight gain [145].

3.2.1.3.4. Phenytoin. Phenytoin is an anticonvulsant that blocks voltage-dependent membrane sodium channels [146]. Phenytoin has

Table 2
The effect of different medications for chronic pain on body weight.

Chronic Pain					
Medication Group	Medication	Weight Gain	Weight Neutral	Weight Loss	Reference
Analgesics	Acetaminophen		?		
NSAIDs	All		?		
TCAs	All	X	X		[164]
SNRIs	All	X			[67]
Anticonvulsants	Gabapentin	X			[165]
	Pregabalin	X			[]
	Carbamazepine	X			[]
	Phenytoin		X		[166]
	Topiramate			X	[167]

Title: The effect of different medications for chronic pain on body weight.
X: <5% of total body weight change.
NSAIDs: Nonsteroidal Anti-inflammatory Drugs; TCAs: Tricyclic Antidepressants; SNRIs: Serotonin-Norepinephrine Reuptake Inhibitors.

been reported to be weight neutral in several studies and reviews [19,147,148]. Chen et al. reported in their study a relatively stable weight after phenytoin initiation when compared to other anticonvulsants such as pregabalin and valproic acid [149].

3.2.1.3.5. Topiramate. Topiramate is an anticonvulsant medication that blocks the voltage-gated sodium channels and is indicated for epilepsy and migraine prophylaxis [150]. The combination of phentermine/topiramate (Qsymia) is an FDA-approved drug for weight loss [151]. A proposed mechanism is that topiramate reduces caloric intake by appetite suppression through the modulation of GABA receptors [152,153] or via the effects of carbonic-anhydrase inhibition on taste [154]. Another proposed mechanism includes activation of protein kinase and acetyl-coenzyme A carboxylase phosphorylation which enhances the energy metabolism in peripheral tissues [155]. In a meta-analysis consisting of 10 RCTs with a total of 3320 patients using topiramate, significant weight loss was reported with a mean average of 5.34 kg (95%CI -6.12 to -4.56 kg) [156]. In another RCT comparing the use of topiramate and gabapentin in migraine prophylaxis, both drugs were equally effective in migraine prophylaxis [157]. However, weight gain was a common side effect associated with gabapentin (7.5% of patients) while weight loss was linked to topiramate (22.5% of patients) [157].

3.2.2. Expert opinion: weight-centric approach

When treating chronic pain, it is important to pay close attention to the medications that can be used. The side effect profile of these medications can play a major role in prescribing one rather than another drug. For example, some important and serious side effects include pancreatitis associated with topiramate [158], agranulocytosis and aplastic anemia with carbamazepine [159], and hepatic toxicity with valproic acid [160]. Thus, the medication used to treat any chronic pain must be tailored to each patient, taking into account contraindications and side effects associated with these drugs.

3.2.2.1. Weight-centric management. For patients with overweight or obesity, prescribers should try to avoid initiating/continuing medications that are known to increase body weight (e.g., TCAs, most anticonvulsants) and switch to medications with weight neutral/loss effect (e.g., topiramate and NSAIDs) (Table 2). In a systematic review on obesity and chronic pain, a major barrier to effective lifestyle modification and rehabilitation was reported to be inadequate pain control. In addition, weight reduction was shown to alleviate pain and reduce pain-related functional impairment [161]. Thus, obesity and chronic pain are significantly linked in which the treatment of each one of these conditions may depend on the management of the other. On the other hand, patients with anorexia nervosa can benefit from medications that do not make them lose more weight. In fact, several case reports found that topiramate may trigger the occurrence of eating disorders including anorexia nervosa in susceptible patients [162,163]. Hence, the effect of these medications on weight gain/loss is important to consider when prescribing for patients with weight-related problems/comorbidities.

4. Conclusion

In conclusion, body weight management is a critical step in preventing and treating variable CNCD associated with overweight and obesity (i.e., depression and chronic pain). However, some medications used for conditions that are more prevalent in patients with overweight or obesity (e.g., depression, chronic pain [15,30]) can contribute to more weight gain. Taking this into consideration, and the challenges associated with helping patients with overweight and obesity to achieve weight loss [168] necessitate physicians to follow a weight-centric approach while treating such common medical conditions. By shifting prescribing practices toward a weight-centric approach, it is possible that the incidence of overweight and obesity caused by these medications can be mitigated. Nonetheless, more research (e.g., RCTs) is needed to further understand the effect of these medications on body weight.

Ethical review

The submission represents original work. The submission does not involve any human test subjects or volunteers.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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