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Gender-related issues in the pharmacology of new anti-obesity drugs

Mauro Cataldi[1,4] | Giovanna Muscogiuri[2,4] | Silvia Savastano[2,4] | Luigi Barrea[2,4] | Bruna Guida[3,4] | Maurizio Taglialatela[1,4] | Annamaria Colao[2,4]

[1] Division of Pharmacology, Department of Neuroscience, Reproductive Sciences and Dentistry, Federico II University of Naples, Naples, Italy

[2] Division of Endocrinology, Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples, Italy

[3] Division of Physiology, Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples, Italy

[4] Federico II University Hospital, Naples, Italy

Correspondence
Professor Annamaria Colao, Division of Endocrinology, Department of Clinical Medicine and Surgery, Federico II University of Naples, Via Sergio Pansini 5, Naples 80131, Italy.
Email: colao@unina.it

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Summary

Four new medicines—liraglutide, lorcaserin, bupropion/naltrexone, and phentermine/topiramate—have been recently added to the pharmacological arsenal for obesity treatment and could represent important tools to manage this epidemic disease. To achieve satisfactory anti-obesity goals, the use of these new medicines should be optimized and tailored to specific patient subpopulations also by applying dose adjustments if needed. In the present review, we posit that gender could be among the factors influencing the activity of the new obesity drugs both because of pharmacokinetic and pharmacodynamic factors. Although evidence from premarketing clinical studies suggested that no dose adjustment by gender is necessary for any of these new medicines, these studies were not specifically designed to identify gender-related differences. This observation, together with the strong theoretical background supporting the hypothesis of a gender-dimorphic response, strongly call upon an urgent need of new real-life data on gender-related difference in the pharmacology of these new obesity drugs.

KEYWORDS

liraglutide, lorcaserin, naltrexone/bupropion, phentermine/topiramate

1 | INTRODUCTION

Obesity is a gender dimorphic disease.[1] Indeed, there are differences in its prevalence, pathophysiology, clinical presentation, and natural history between men and women. The worldwide prevalence of obesity is higher in women than in men (15% vs 11% in 2016).[2] Excess fat distribution is also different between males and females, being concentrated mainly in centrally located visceral areas in men and subcutaneously in women.[3] Moreover, obesity increases cardiovascular risk more in men than women, possibly because visceral fat worsens insulin resistance, lipid profile, and fluid metabolism much more than subcutaneous fat.[1]

Nevertheless, very few studies addressed the question of whether gender also contributes to the response to anti-obesity treatment. A meta-analysis of 58 published studies[4] showed a higher decrease in body weight in response to diet and lifestyle changes in men than in women, although the weight loss difference was small. Likewise, body weight decreased more in men than in women in about 50% of the studies on bariatric surgery, lifestyle, or diet treatment examined by Stroebele-Benschop et al,[5] whereas no gender difference emerged in the remaining. The systematic review published by Robertson et al[6] as part of the ROMEO (Review Of MEn and Obesity) study also reported gender-related differences in therapeutic responses, with men responding better to some interventions and women to others.

For years, the only approved drugs for the treatment of obesity have been amphetamines and orlistat in the United States and orlistat

Abbreviations: AgRp, Agouti-related peptide; AMPK, AMP-kinase; CRH, corticotropin releasing hormone; DAT, Dopamine transporter; DEA, Drug Enforcement Administration; EMA, European Medicinal Agency; ER, oestradiol receptors; FDA, Food and Drug Administration; FMO, flavin mono-oxygenase; Kir, inwardly rectifying K^+ channels; MEK, MAP kinase/ERK kinase; NAc, nucleus accumbens; NET, noradrenaline transporter; PIP_2, phosphatidylinositol 4, 5-bisphosphate; POMC, proopiomelanocortin; RCT, randomized clinical trials; TRH, thyrotropin releasing hormone; VTA, ventral tegmental area

only in Europe. Gender differences have not been systematically investigated in the case of amphetamines, whereas conflicting results have been obtained with orlistat.[7-9] In the last years, four new prescription drugs enriched the pharmacological arsenal against obesity in the United States: liraglutide, lorcaserin, bupropion/naltrexone, and topiramate/phentermine.[10] Two of these medicines, liraglutide and bupropion/naltrexone, have been approved also by the European Medicines Agency (EMA) and are thus already available for clinical use in some countries of the European Community. The gender dependence of the clinical response to these new drugs has been only marginally investigated. However, as described in Figure 1 and extensively reported in the next sections, both pharmacodynamic (Table 1) and pharmacokinetic (Table 2) arguments suggest that gender could significantly influence the effect of these new medicines.

2 | LIRAGLUTIDE

Liraglutide is a glucagon-like peptide 1 (GLP1) derivative that differs from human GLP1 because of the substitution of a lysine at position 34 and of the binding of a palmitic acid fatty chain to lysine 26 through a glutamic acid spacer.[48] Because of these modifications, liraglutide is more stable than GLP1 in plasma and strongly binds to plasma proteins. Liraglutide has been originally approved for the treatment of type II diabetes. Because a substantial weight loss was noticed in patients with diabetes treated with this drug, the hypothesis that liraglutide could be used for weight reduction in patients with obesity was raised and formally demonstrated in randomized clinical trials finally leading to its approval as an anti-obesity drug.[67,68] The retrospective analysis of these preregistration clinical trials showed that liraglutide-induced weight loss was larger in women than in men at all dosages up to 3 mg; importantly, in men the dose-response curve did not plateau at this concentration, suggesting that men could be less sensitive to liraglutide than women.[49] Both pharmacodynamic and pharmacokinetic factors could be responsible for this gender-related difference as detailed in the next sections.

2.1 | Pharmacodynamics

Liraglutide pharmacodynamics is very complex because this drug acts at different levels to affect glucose homeostasis, pancreatic ß-cells survival, insulin secretion, and feeding behaviour. Liraglutide acts by interacting with Gs-coupled GLP-1 receptors (GLP-1R), which belong to the GPCR B1 subfamily (secretin receptor family).[11] GLP-1R is part of a multimolecular complex that includes the progesterone receptor membrane component 1 (PRMC1), a member of the membrane-associated progesterone receptor protein family.[12] Although it is still unclear whether PRMC1 may transduce physiologically relevant progesterone-dependent signals, the evidence that a progesterone binding protein is physically associated to the GLP-1R represents a first hint that sex steroids could modulate GLP-1 activity. Additional indications of a possible role of gender in GLP-1 physiology are that progesterone induces GLP-1 secretion in cultured enteroendocrine cells in vitro and in mice in vivo[13] and that testosterone enhances insulin secretion in pancreatic ß-cells by potentiating GLP-1 signal transduction at a postreceptor level in a cAMP/PKA dependent manner.[14]

The anorexigenic effect of GLP-1 agonists is exerted at the level of the central nervous system where GLP-1 physiologically controls the activity of brain regions involved in feeding behaviour. Among them, a crucial role has been attributed to the arcuate nucleus where GLP-1 directly stimulates anorexigenic proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons and indirectly inhibits orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons.[69] In addition, GLP-1 and GLP-1R agonists are also involved in the control of food reward through GLP-1Rs expressed

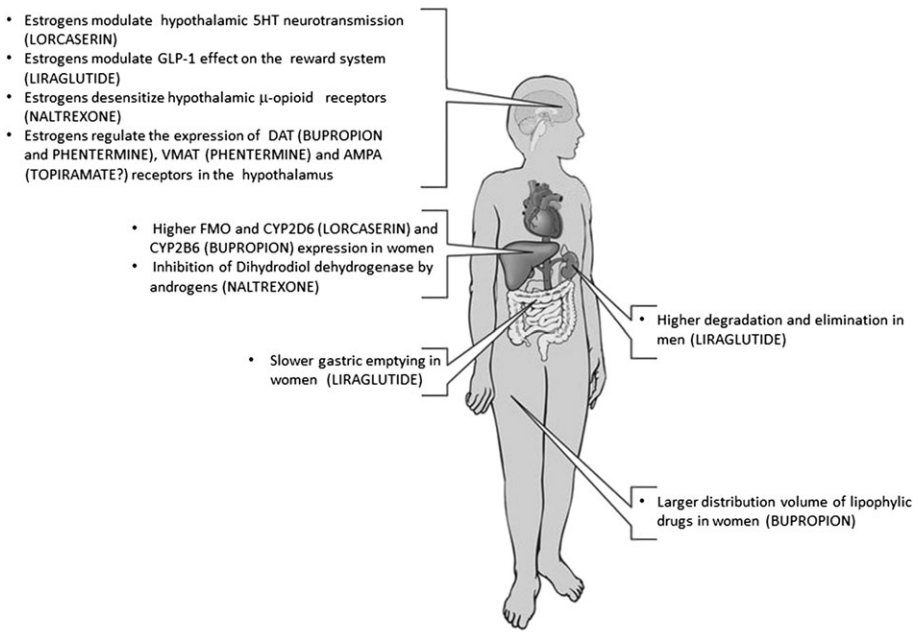

FIGURE 1 Schematic representation of the mechanisms potentially contributing to gender-related differences in the activity of the anti-obesity drugs at each anatomical site

TABLE 1 Mechanisms of action of the new anti-obesity drugs: Influence of gender-related factors

	Mechanism of Action	Gender-Related Factors	References
Liraglutide	Activation of anorexigenic POMC/CART neurons Inhibition of orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons Reduced food reward Slowing of gastric emptying	Association of plasma membrane progesterone receptors to GLP1 receptor in a multimolecular complex Progesterone control of GLP-1 release in humans GLP-1 dependent androgen control of insulin secretion Oestrogen-dependence of central exendin anorectic effect Gender difference in gastric emptying	11-17
Lorcaserin	Stimulation of anorexigenic POMC/CART neurons	Oestradiol-dependent modulation of serotoninergic neurotransmission at multiple levels (serotonin synthesis and expression of serotonin receptors and transporters) The anorectic effect of serotoninergic drugs in experimental animals is oestrogen-dependent	18-28
Naltrexone/bupropion combination			
Naltrexone	Blockade of μ-opioid receptors on POMC neurons Blockade of β-endorphin autofeedback on POMC neurons	Oestradiol-dependent desensitization of μ-opioid receptors in anorexigenic hypothalamic POMC neurons Gender difference in the hypothalamic–pituitary–adrenal axis response to naltrexone Gender difference in the clinical response to naltrexone in alcohol dependence	29-33
Bupropion	Central anorexigenic effects: Inhibition of DA and NE reuptake Stimulation of POMC neurons in the arcuate nucleus	Oestradiol-dependent regulation of the expression of both DAT and D2 receptors Oestradiol-mediated potentiation of bupropion antidepressant effect	34-39
Phentermine/topiramate combination			
Phentermine	Enhanced DA and NE release in the hypothalamus by the combined blockade of DAT, NET, VMAT, and MAO	Oestrogen-dependent regulation of MAO, NET, DAT, and VMAT expression Higher NE-induced lipolysis in women	40-43
Topiramate	Potentiation of leptin and insulin signalling in the hypothalamus Enhancement of insulin sensitivity in skeletal muscles	Oestrogenic control of AMPA receptor expression	44-47

in the ventral tegmental area (VTA) and in the nucleus accumbens (NAc), key nodes of the central reward circuitry.[70] Functional magnetic resonance imaging (fMRI) studies showed that other brain regions such as insula, amygdala, and orbitofrontal cortex are also involved in food reward mechanisms and that their activation in response to food pictures is strongly reduced by the administration of GLP-1 antagonists.[71] Evidence is starting to accumulate that central GLP-1 effect could be modulated by sex steroids. For instance, Richard et al[72] showed that female rats are more sensitive than males to the anorexigenic effect of a centrally administered GLP-1R agonist (exendin-4) and that this gender difference is abrogated by antioestrogens. The oestrogen modulation of GLP-1 anorexigenic activity could involve VTA and NAc considering that the anorexigenic effect of oestradiol is at least in part exerted at the level of these brain structures.[15]

An additional mechanism of liraglutide anorexigenic effect is the ability of this drug to activate gastric vagal afferents, thereby slowing gastric emptying and promoting an early sense of satiety via central mechanisms.[16] Although it is well established that gastric emptying is slower in women than in men,[17] no study has yet addressed the gender-dependence of liraglutide effect on this process.

2.2 | Pharmacokinetics

Data from preregistration clinical trials showed that liraglutide exposure was about 32% higher in women than in men after adjusting for body weight; although the mechanism involved was not directly investigated, a higher rate of drug degradation in men when compared with women may explain this phenomenon.[50] Noteworthy, this difference in liraglutide disposition could account for about 50% of the greater weight loss induced by 3-mg liraglutide in women when compared to men.[49]

3 | LORCASERIN

Lorcaserin is a highly specific agonist of the $5HT_{2C}$ receptors, the receptor subtype responsible for serotonin anorectic effect.[18] In fact, lorcaserin reduces appetite without triggering valvular heart defects or pulmonary hypertension, both serious unwanted effects associated to the stimulation of other serotonin receptors and which led to the withdrawal from the market of the old anorectic serotonin reuptake inhibitor d-fenfluramine.[18]

Lorcaserin was approved by the Food and Drug Administration (FDA) in 2012 based on the results of three randomized clinical trials (RCT) that enrolled both men and women. These RCT, not specifically designed to investigate gender differences, did not find any difference in lorcaserin response between males and females and therefore, no gender-related adjustment was deemed necessary with this drug.[73,74] In contrast with these findings, Anderson et al[75] reported that men lose more weight than females while on lorcaserin, whereas Kolotkin et al[76] found a higher improvement in quality of life

TABLE 2 Pharmacokinetics of new anti-obesity drugs: Influence of gender-related factors

	PK profile	Gender-Related Factors	References
Liraglutide	Subcutaneous administration Slow absorption from the injection site Strong plasma protein binding (>98%) Small distribution volume Degraded in small peptides Clearance: 1.2 L/h Half-life: 13 h	Drug exposure about 32% higher in women than in men Higher drug degradation in men (?)	48-50
Lorcaserin	Oral administration T_{max}: 1.5-2 h Liver metabolism to inactive metabolites by CYP3A4, CYP2D6 and FMO Metabolites eliminated with urines Half-life: 1.8 h Available as an extended release formulation for one-daily administration	Higher CYP2D6 and FMO expression in women	51-54
Naltrexone/bupropion combination			
Bupropion	Oral administration T_{max}: 3 h Strong plasma protein binding (>80%) Large distribution volume with accumulation in the adipose tissue Liver metabolism by CYP2B6 to the active metabolite hydroxy-bupropion Urinary elimination	Higher CYP2B6 expression in women Higher drug exposure in women among patients treated for depression or smoking cessation	34,55-57
Naltrexone	Oral administration High hepatic first pass effect and low oral bioavailability (5-40%) Low plasma-protein binding (~20%) Large distribution volume (1350 L) with accumulation in the brain, spleen, and adipose tissue Liver metabolism by dihydrodiol dehydrogenase to the active metabolite 6β-naltrexol Half-life: 4 h Clearance: 3.5 L/min	Inhibition of dihydrodiol dehydrogenase by androgens that are also substrates of this enzyme Higher naltrexone and 6β-naltrexol concentrations in women Higher naltrexone to 6β-naltrexol ratio in women	34,58-61
Phentermine/topiramate combination			
Topiramate	Oral administration High oral bioavailability (>80%) T_{max}: 1.8-4.3 h An extended release formulation with longer T_{max} is available and used in the combination with phentermine Half-life: 19-23 h Low plasma protein binding (13-17%) Distribution volume: 0.6-0.80 L/kg Most of the drug is excreted unmodified in the urine	Higher drug exposure in female than in male rats Values of distribution volume for females about 50% of those for males	62,63
Phentermine	Oral administration High oral bioavailability T_{max}: 3-4.4 h Low plasma protein binding Distribution volume: 3-4 L/kg Most of the drug (62.7-84.8%) excreted unmodified in the urine	No data available	64-66

in female than in male patients with obesity primarily because of a larger effect on BMI. While the the existence of a gender difference in the clinical response to lorcaserin is still debated, intrinsically gender-dimorphic pathophysiological mechanisms seem to be targeted by this drug, as discussed in the next section.

3.1 | Pharmacodynamics

As mentioned before, lorcaserin acts by selectively potentiating the serotoninergic neurotransmission at postsynaptic $5HT_{2C}$ receptors. Intriguingly, serotoninergic neurotransmission is also modulated by oestradiol, which has a significant anorectic effect in rats,[58] and this sex hormone influences the anorectic effect of serotoninergic drugs. Indeed, in female rats, low fenfluramine doses decrease food intake only when given during estrus but not during diestrus,[19] and in ovariectomized rats, this anorectic effect is increased by the administration of oestradiol benzoate.[20] The oestradiol-dependent enhancement of serotonin anorectic effect is explained by the ability of this hormone to potentiate the serotoninergic neurotransmission at different levels. In fact, oestrogen receptors are expressed in serotoninergic neurons[21] and oestradiol increases the expression of tryptophan hydroxylase and decreases the expression of serotonin transporters in midbrain serotoninergic neurons.[22,23] Oestradiol increases the expression of serotonin $5HT_{1A}$ and $5HT_{2A}$ receptors, two effects mediated by different oestradiol receptors (ER), ERα and ERβ, respectively,[24,25] while conflicting results have been obtained on $5HT_{2C}$ expression in the hypothalamus.[26-28] In addition, Rivera et al[28] suggested that oestradiol

could potentiate the anorectic effect of selective $5HT_{2C}$ agonists by increasing the expression of $5HT_{2C}$ receptors in the caudal hindbrain and not in the hypothalamus, whereas Qiu et al[78] hypothesized that oestradiol and serotonin could interact at a postreceptor level. More specifically, these authors demonstrated that both oestradiol and $5HT_{2C}$ agonists reduce the ability of the $GABA_B$ agonist baclofen to activate G-protein–coupled inwardly rectifying K^+ channels (Kir) in POMC neurons of the arcuate nucleus and speculated that the activity of these neurons could be enhanced in vivo by a similar effect, namely, the attenuation of tonic $GABA_B$-dependent inhibition.[79] The molecular mechanism responsible for both serotonin- and oestrogen-dependent attenuation of $GABA_B$-dependent Kir activation seems to involve the depletion of plasma membrane phosphatidylinositol 4,5-bisphosphate (PIP_2), possibly triggered by activation of Gq-coupled plasma membrane receptors.[79]

In conclusion, there is evidence that, at least in the rat, oestradiol and serotonin $5HT_{2c}$ receptors control feeding via a converging signalling mechanisms, thus establishing a robust rationale for possible gender-related effects in the action of lorcaserin.

3.2 | Pharmacokinetics

The pharmacokinetics of lorcaserin is summarized in Table 2 and more details can be found in previous studies.[51,52] Two of the main enzymes involved in the metabolism of lorcaserin, CYP2D6 and flavin monooxygenase (FMO), have a higher expression in women than in men; however, the impact of this gender difference on lorcaserin metabolism remains to be investigated.[53,54] However, preregistration population pharmacokinetic studies, though not specifically designed to identify gender differences, showed that lorcaserin disposition was affected by body weight, the presence of diabetes, and the drug formulation used but not by gender.[51]

4 | NALTREXONE/BUPROPION COMBINATION

Bupropion and naltrexone are marketed as a combination in a single medicine to take advantage of their pharmacological synergism in suppressing appetite and lowering body weight.[34] A higher body weight–lowering effect was observed in females in preregistration clinical trials, but no gender-related dose adjustment was deemed necessary by regulatory agencies.[80] Both pharmacodynamic and pharmacokinetic factors could account for gender-related differences in the activity of this drug combination.

4.1 | Pharmacodynamics

Bupropion is an antidepressant that is structurally related to the indirect sympathetic agonist diethylpropion and blocks the presynaptic transporters for dopamine (DAT) and noradrenaline (NET).[34,35] The consequent increase in the concentration of these transmitters at the synaptic cleft in the hypothalamus is responsible for bupropion anorectic effect.[36] Indeed, dopaminergic and noradrenergic terminals located in the arcuate and in the paraventricular nuclei control hunger and satiety.[81,82] Most of the effects of hypothalamic monoaminergic systems on feeding are supposed to converge on the regulation of POMC neurons that represent key mediators of anorexigenic responses.[83] An additional mechanism by which bupropion-induced enhancement of dopaminergic neurotransmission could elicit an anorectic response is the regulation of the central reward pathways, as suggested by the ability of dopaminergic antagonists to abrogate the anorectic effect of diethylpropion when infused into the NAc.[84]

The evidence that the expression of dopamine receptors and transporters in the central nervous system is strongly modulated by sex steroids represents a theoretical premise for a possible gender dimorphic response to bupropion. It has been reported, indeed, that, in rats, ovariectomy lowers the expression not only of D_2 dopamine receptors but also of DAT in the NAc, caudate nucleus, and in the cingulate cortex, whereas chronic treatment with oestrogens reverts these changes.[37] In neurons, oestrogens also directly enhance DAT activity in a protein kinase C (PKC)- and MAP kinase/ERK kinase (MEK)-dependent manner.[38] An additional mechanism by which oestrogens further enhance dopamine uptake in neurons is the increase in the availability of this neurotransmitter for neuronal DAT through the inhibition of its astrocytic uptake.[85] Although the effect of oestrogens on the anorexigenic mechanism of bupropion has not been investigated so far, published data demonstrate that these hormones do potentiate the antidepressant activity of this drug.[39]

Naltrexone, the other component of the bupropion/naltrexone combination, is an orally active antagonist of μ-, κ-, and δ-opioid receptors approved for the treatment of opioid and alcohol addiction.[29,86] Although the endogenous opioid system controls feeding behaviour and opioid agonists and antagonists, respectively, increase and decrease feeding in experimental animals,[87] naltrexone was not added to bupropion in the naltrexone/bupropion combination to take advantage of its weak anorectic activity in humans.[88] Instead, the pharmacological synergism of naltrexone with bupropion is related to the ability of naltrexone to counteract an opioid-dependent feedback mechanism that limits the effect of bupropion on POMC-neurons.[30,31] This autoinhibitory mechanism physiologically regulates POMC-neuron activity through the release of the POMC derivative β-endorphin which activates μ-opioid receptors,[89] as also indicated by the increase in POMC gene expression in the hypothalamus that occurs when opioid receptors are chronically blocked with naltrexone.[90]

It is expected that this mechanism by which naltrexone increases bupropion anorectic effect could show gender-related differences. Indeed, it has been clearly demonstrated that μ-opioid receptors in the hypothalamus are modulated by oestrogens. More precisely, oestradiol desensitizes μ-opioid receptors in anorexigenic hypothalamic POMC neurons upon binding to plasma-membrane Gq-mER receptors.[91,92] This effect is exerted downstream the opioid receptor and does not involve changes in ligand affinity.[92] Although whether oestradiol modifies the response to naltrexone/bupropion in obesity still needs to be established, gender-related differences have been reported for other effects of naltrexone such as the acute stimulation of the hypothalamic-pituitary-adrenal axis[32] or alcohol weaning.[33] New information on the mechanism responsible for the central anorexigenic effect of the naltrexone/bupropion combination are beginning to emerge from fMRI studies; using this technique, Wang et al[93] showed

that the naltrexone/bupropion combination attenuates the activation of the hypothalamus in response to food visual cues while enhancing at the same time the activation of cortical regions involved in inhibitory control (anterior cingulate), internal awareness (superior frontal, insula, superior parietal), and memory (hippocampal). These data, therefore, support the idea that, in humans, additional regions besides those identified in rodents are modulated by the naltrexone/bupropion combination, yielding to a much more complicated scenario than initially thought, whose modulation by gender remains to be investigated.

4.2 | Pharmacokinetics

The main pharmacokinetic properties of bupropion and naltrexone are summarized in Table 2 and further details can be found in Jefferson et al[94] and Bullingham et al.[58]

Gender could affect bupropion pharmacokinetics at the level of both drug metabolism and distribution. Bupropion is hydroxylated in the liver to its active metabolite hydroxy-bupropion by CYP2B6 that is, indeed, potently induced by oestrogens as also indicated by its higher levels in females as compared with males.[55,56] Although oestrogen-dependent CYP2B6 induction may decrease drug exposure in women as compared with men, other gender-related factors can counterbalance this effect. More specifically, bupropion accumulates in fat because of its high lipophilicity, and therefore, drug AUC tends to be higher in women than in men.

The hypothesis that gender-related differences may influence the pharmacokinetics of bupropion has been already examined in past studies with controversial results. For instance, while Findlay et al[95] did not find any difference between sexes in bupropion pharmacokinetics, Stewart et al[57] observed a different bupropion and hydroxyl-bupropion pharmacokinetic profile in male and female adolescents taking bupropion for smoking cessation. They found that the AUC and C_{max} of both bupropion and hydroxy-bupropion were significantly higher in females than in males. Interestingly, bupropion distribution volume and half-life were both higher in females than in males whereas no difference was observed in drug clearance. More recently, Laib et al[96] performed a cross-sectional study among depressed patients treated with bupropion with the aim of validating an HPLC technique for the therapeutic drug monitoring of this antidepressant through the measurement of hydroxy-bupropion plasma levels. The results of this study seem to confirm the hypothesis of a significant gender dimorphism in bupropion pharmacokinetics because higher bupropion plasma levels were found in female than in male patients.

Gender-related differences in naltrexone pharmacokinetics have also been reported. In patients taking this drug as an adjunct to nicotine patch for smoking cessation, the plasma concentrations of the main naltrexone metabolite 6β-naltrexol, which has about a half potency of the parental compound in blocking μ-opioid receptors, were higher in women than in men.[59] Similar results were obtained by Liu et al[60] in patients with chronic pain taking naltrexone for opioid weaning. A possible explanation for these findings is that testosterone and dihydrotestosterone are both substrates and the most potent competitive inhibitors of dihydrodiol dehydrogenases responsible for naltrexone conversion into 6β-naltrexol.[61]

The effect of gender on the plasma levels of bupropion, hydroxybupropion, erythrohydrobupropion, threohydrobupropion, naltrexone, and 6β- naltrexol after the administration of the bupropion/naltrexone combination have been examined in the Clinical Pharmacology and Biopharmaceutics Review(s) of the FDA new drug application for this medicine.[97] A significant effect of gender was found on the ratio between bupropion clearance (Cl) and bioavailability (F) (Cl/F), but it was considered too small to warrant gender-related dose adjustment.

5 | PHENTERMINE/TOPIRAMATE COMBINATION

A fixed combination of phentermine and extended release topiramate has been approved by the FDA[98] in 2012, whereas the EMA refused its marketing authorization because of safety concerns.[99] Both these drugs cause weight loss even when administered separately and no formal demonstration of a real synergism between them has been obtained so far.[100] The reason why phentermine and topiramate have been combined in a single pill is related to their different pharmacokinetics: Phentermine acts rapidly but for a short time, whereas topiramate activity has a slower onset but a longer duration; therefore, by combining phentermine and topiramate a prolonged clinical effect can be obtained.[101] Data from preregistration clinical trials showed that "the treatment effect of phentermine/topiramate on percent weight loss was numerically larger for women."[102]

5.1 | Pharmacodynamics

Topiramate is a sulfamate-substituted monosaccharide currently approved for epilepsy and for migraine prophylaxis whose ability to induce weight loss was fortuitously discovered in clinical trials evaluating the drug in the aforementioned indications.[103] Topiramate has a very complex pharmacology as it affects multiple targets whose relevance in determining specific drug effects is often unclear. More specifically, it blocks neuronal voltage-gated Na^+ and Ca^{2+} channels and AMPA/kainate receptors, increases the activity of $GABA_A$ receptors and inhibits carbonic anydrase.[104] The weight-lowering mechanism of topiramate remains uncertain, but seems to involve both central and peripheral targets. Topiramate acts peripherally by enhancing insulin sensitivity and activating AMP-kinase (AMPK) and acetyl-CoA carboxylase in skeletal muscles,[44,45] whereas its central effect is mainly exerted in the hypothalamus where it potentiates both leptin-induced Jak-Stat and MAPK/ERK and insulin-induced insulin receptor substrate/Akt/forkhead box O1 pathway activation.[46] These effects on leptin and insulin signalling ultimately lead to an increase in the transcription of genes encoding for anorectic peptides including POMC, thyrotropin-releasing hormone (TRH), and corticotropin-releasing hormone (CRH).[46] Topiramate-induced AMPA receptor inhibition could also have a role in the anorectic activity of this drug considering that the stimulation of hypothalamic AMPA receptors induces feeding in rats.[105] The evidence that oestrogens control hypothalamic AMPA receptor expression[47] suggests that topiramate anorectic efficacy could be different between men and women.

However, gender differences have been reported so far only in its efficacy in stopping smoking addiction,[106] but not for other topiramate effects also including the decrease in body weight observed in epileptic patients.[107]

Phentermine is a substituted amphetamine, and as such, it increases adrenergic and dopaminergic neurotransmission by the inhibition of noradrenaline and dopamine recapture and the promotion of their presynaptic release.[108] Therefore, phentermine anorectic effect can be ultimately explained by an enhancement of catecholaminergic hypothalamic neurotransmission as described before for bupropion. Peripheral lipolytic effects also contribute to phentermine-induced weight loss. Addiction potential is believed to be significantly lower with phentermine than with other amphetamines,[109] and therefore, the US Drug Enforcement Administration (DEA) included this drug in schedule IV of addiction substances. Phentermine was approved by the FDA for human obesity in 1959 and still ranks among the first 200 more prescribed drugs in the United States[110] in 2018. On the contrary, amphetamines cannot be used for obesity in EU countries because they have been banned for their cardiovascular toxicity and addiction potential.

Sex steroids modulate the expression of monoamino-oxidases, noradrenaline and dopamine transporters, and vesicular monoamine transporters,[40-42] and this could account for the gender differences observed in amphetamines and cocaine psychostimulant effect.[111,112] It is well established, indeed, that the addiction potential of these drugs is higher in females than in males both in experimental animals and in humans.[113] Gender differences in body weight response to amphetamines have not been systematically explored. However, the anorectic response to methylphenidate, a psychostimulant that shares with amphetamines the ability to block NET and DAT,[114] seems to differ between genders. For instance, treatment with this drug lowers body weight faster in male than in female rats and reduces total fluid intake in male only.[115] In addition, in normal-weight humans, methylphenidate decreases energy intake more in men than in women,[116] whereas in patients with obesity, it significantly reduces appetite, cravings, and snack-food intake only in women.[117] A stronger anorectic effect in women than men has been observed in the response to methylphenidate also in binge eating disorders.[118] Finally, a tendency for a greater weight loss in women than in men was observed in a recent pilot study that explored the effect in obesity of dexamphetamine, an amphetamine approved in 2015 by FDA for the treatment of binge eating disorders.[116] Not only the central anorectic but also the peripheral effect of amphetamines could be gender-related as suggested by the evidence that the infusion of moderate doses of epinephrine and/or norepinephrine induces a larger lypolytic effects in women than in men.[43]

5.2 | Pharmacokinetics

Studies on the pharmacokinetics of topiramate and phentermine given together in a single pill have been performed as part of the preapproval characterization of this new medicine.[62,119] These studies showed that phentermine does not affect topiramate pharmacokinetics, whereas topiramate does increase phentermine exposure in rats and men but not in dogs. No gender-related difference in phentermine pharmacokinetics was observed in dogs, whereas in rats, the exposure to topiramate was higher in females possibly because the drug is less metabolized than in males.[62,120] Although in humans the distribution volume of topiramate given alone is about twofold higher in males than in females,[63] population pharmacokinetic studies did not show any significant effect of gender on the exposure to either phentermine or topiramate after the administration of the combined pill, and based on these pharmacokinetic findings, the FDA reviewers did not recommend any dose adjustment based on gender.[119]

6 | CONCLUSION

In the present work, we have reviewed the available evidence on gender dimorphism in the pharmacology of new anti-obesity drugs. Many pharmacokinetic and pharmacodynamic factors stand out as potentially responsible for relevant gender-related differences in the effects of these drugs. Nonetheless, the clinical trials performed so far, though enrolling both men and women, were not specifically designed to identify gender-related differences, as these were explored only as a covariate, leading to the perception that no gender-dependent adjustment is necessary. On the basis of the issues herein highlighted, gender-related differences in the efficacy and toxicity of these drugs need to be urgently explored with specifically designed real-life studies. Given the great social relevance of obesity therapeutics, the identification of gender related variables is likely to allow precise patient stratification to improve personalized pharmacological treatment with these new drugs.

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CONFLICT OF INTEREST

No conflict of interest was declared.

ORCID

Mauro Cataldi http://orcid.org/0000-0001-7787-3406
Giovanna Muscogiuri http://orcid.org/0000-0002-8809-4931
Maurizio Taglialatela http://orcid.org/0000-0002-8202-0560

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