Opioid antagonism mitigates antipsychotic-associated weight gain: focus on olanzapine

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Abstract

Background. The endogenous opioid system affects metabolism, including weight regulation. Evidence from preclinical and clinical studies provides a rationale for targeting this system to mitigate weight-related side effects of antipsychotics. This review describes the role of the opioid system in regulating weight and metabolism, examines the effects of opioid receptor antagonism on those functions, and explores the use of opioid antagonists to mitigate antipsychotic-associated weight gain and/or metabolic effects.

Methods. A PubMed literature search was conducted to identify representative opioid antagonists and associated preclinical and clinical studies examining their potential for the regulation of weight and metabolism.

Results. The mu opioid receptor (MOR), delta opioid receptor (DOR), and kappa opioid receptor (KOR) types have overlapping but distinct patterns of central and peripheral expression, and each contributes to the regulation of body weight and metabolism. Three representative opioid antagonists (eg, naltrexone, samidorphan, and LY255582) were identified for illustration. These opioid antagonists differed in their receptor binding and pharmacokinetic profiles, including oral bioavailability, systemic clearance, and half-life, and were associated with varying effects on food intake, energy utilization, and metabolic dysregulation.

Conclusions. Preclinical and clinical data suggest that antagonism of the endogenous opioid system is a mechanism to address antipsychotic-associated weight gain and metabolic dysregulation. However, evidence suggests that the differing roles of MOR, DOR, and KOR in metabolism, together with the differences in receptor binding, pharmacokinetic, and functional activity profiles of the opioid receptor antagonists discussed in this review, likely contribute to their differential pharmacodynamic effects and clinical outcomes observed regarding antipsychotic-associated weight gain.

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Background

Pharmacologic agents are the cornerstone of treatment for schizophrenia and bipolar I disorder, with atypical antipsychotics representing a first-line treatment option.[1-5] Treatment with many atypical antipsychotics is associated with an increased risk of weight gain and adverse metabolic effects; however, the magnitude of observed effects varies among different agents.[6,7] Olanzapine is associated with a lower rate of all-cause discontinuation, as well as discontinuation owing to inefficacy, compared with other atypical antipsychotics,[8-11] but it is associated with a significant risk for weight gain and metabolic sequelae.[8-13] In clinical trials and population-based studies, treatment with olanzapine was associated with both short-term and long-term increases in weight, waist circumference, and body mass index (BMI), along with an increased risk for dyslipidemia and glucose dysregulation.[7,8,14-16] For some patients, these weight and metabolic consequences may offset the clinical benefits of olanzapine despite its established value as a highly efficacious medicine.

Although the effects of olanzapine on a range of measures related to body weight and metabolic function have been characterized in preclinical and clinical studies, the mechanisms underlying these effects are not well established. Research into mechanisms underlying antipsychotic-associated weight gain has focused on receptor interactions involving serotoninergic, dopaminergic, histaminergic, adrenergic, cannabinoid, and muscarinic receptors.[17] Additionally, the endogenous opioid system plays a role in weight and metabolic regulation,[18,19] and evidence from both preclinical and clinical studies provides a rationale for targeting this system to mitigate weight-related side effects of antipsychotic treatment.[19-23]

The aim of this review is to describe the role of the opioid system in regulation of weight and metabolism, and to examine the effects of opioid receptor antagonism on those functions. A PubMed literature search was conducted for preclinical and clinical studies examining the potential effects of opioid receptor antagonism on weight and metabolism. We included

additional search terms that were selected to identify articles assessing opioid antagonists for their potential to mitigate antipsychotic-associated weight gain in general, and olanzapine-associated weight gain and/or metabolic effects specifically, as well as any other effects on weight gain, lipids, insulin, and glucose regulation. This review focuses on 3 identified opioid antagonists (naltrexone, samidorphan, and LY255582) with effects on weight and metabolic dysregulation described in the literature, and how differences in their respective pharmacokinetic profiles, opioid-receptor binding, and functional activity characteristics may underlay differential metabolic treatment effects.

Opioid receptors associated with effects on body weight and metabolism: types, distribution, and function

Three opioid receptor types, mu opioid receptors (μ-ORs; MORs), delta opioid receptors (δ-ORs; DORs), and kappa opioid receptors (κ-ORs; KORs), are distributed throughout the body in both the central nervous system (CNS) and the periphery,[24] where they contribute to multiple functions, including mood and well-being, pain modulation, and reward response, as well as physiological processes such as respiration and endocrine and immune function.[25-27] Each of the 3 receptor types contributes to the maintenance of body weight and metabolic function,[19,20,22,28] but they are differentiated based on their primary associated endogenous peptides (β-endorphin, enkephalins, and dynorphins for MOR, DOR, and KOR, respectively),[25] the distribution of their expression throughout the body,[24,29] and their specific functions with respect to weight and metabolic regulation.[19,20,22,28]

The opioid system influences appetite and satiety via both central reward circuitry[30,31] and the peripheral gastrointestinal neural system.[32,33] Food intake may be modified by opioid receptor agonists and antagonists through effects on palatability or satiety cues,[32-37] and there is evidence for differential involvement of receptor types centrally and peripherally.[33-35,38] Opioid receptors can also influence dietary preference, altering response to salty or fatty foods,[36,37,39-42] and evidence of the involvement of opioid receptors in binge eating and obesity has been reported.[31,43-45] Furthermore, studies in which opioid receptors are inactivated pharmacologically or by genetic deletion (eg, murine knockout models), as well as genotype association studies, provide evidence that the endogenous opioid system is involved in the regulation of body weight and adiposity, with roles in fat and energy utilization and storage[19,20,22,28]; control of insulin secretion, insulin sensitivity, and glucose production[21,28,46,47]; and food intake,[20,48,49] as detailed below.

Opioid receptor distribution

MOR, DOR, and KOR are expressed in both the CNS and periphery, in sites that are associated with regulation of food intake and metabolism.[18,25,28] Distributions in the CNS and periphery are overlapping, but distinct, as illustrated in Figure 1.[24,29,50] In the CNS, opioid receptor expression has been observed in the mesocorticolimbic pathway, which projects from the substantia nigra and ventral tegmental area into the striatum and prefrontal cortex and is associated with dopaminergic reward circuitry.[24,25,50,51] MOR is widely distributed in the human CNS, with the highest levels detected in the cerebellum, nucleus accumbens, caudate nucleus, and prefrontal cortex.[24,52] DOR is highly expressed in the human cerebral cortex, prefrontal cortex, nucleus accumbens,

caudate nucleus, temporal lobe, and hippocampus,[24,29] and the greatest KOR expression has been observed in human prefrontal cortex, ventral tegmental area, nucleus accumbens, and the caudate nucleus.[24,29]

In the periphery, MOR, DOR, and KOR are expressed in tissues that play a role in regulation of metabolic function and body weight, again with distinct patterns of expression for each receptor type.[20,22,24,28,47,53] The 3 receptor types are expressed in pancreas and small intestine with MOR expression delimited to these structures.[24] DOR is also found in lung, heart, kidney, thymus, and skeletal muscle, and KOR is expressed in the lung, heart, kidney, spleen, thymus, skeletal muscle, and liver (Figure 1).[24]

Opioid receptor gene deletion studies

The observed receptor expression patterns suggest that MOR, DOR, and KOR could contribute differentially to the regulation of weight and metabolism and are supported by the observed effects of respective opioid receptor gene deletions from murine knockout models. In high-fat diet models, mice fed a calorie-rich diet have increases in body weight and fat mass over time compared with mice fed a standard laboratory diet.[19,20,22] In this model, genetic deletion of each opioid receptor type resulted in a reduction in fat mass accumulation and diet-associated weight gain compared with that observed in wild-type animals.[19,20,22] However, specific effects of genetic deletion differed for MOR, DOR, and KOR (Figure 2).

Reported effects of MOR deletion in mice fed a standard diet differ across studies. In one set of studies, MOR knockout mice given a standard diet for 180 days after birth had greater weight gain and increased fat tissue compared with wild-type mice.[28] The MOR knockout mice also had enhanced glucose tolerance, which resulted from insulin hypersecretion, although the insulin hypersecretion was not associated with any increased propensity for developing type II diabetes as the MOR knockout mice aged.[28] In a second set of studies, MOR knockout mice fed a standard diet had no increase in body weight, food intake, or total energy expenditure; however, a shift in fuel utilization to relatively greater fat utilization was observed. In contrast to the Wen 2009 study,[28] this second study used only male mice that were 16 to 28 weeks of age at the onset of the study, but the period over which weight gain was assessed was not specified. On a high-fat diet (Figure 2), MOR knockout mice had similar caloric intake and no evidence of a change in metabolic rate, but a significantly lower ratio of body weight gained per kilocalorie consumed, compared with wild-type mice.[22] MOR gene deletion was protective against insulin resistance and glucose intolerance in aging mice fed a high-fat diet, and was associated with the upregulation of enzymes involved in fatty acid oxidation in liver and skeletal muscle, reducing the efficient storage of ingested fat.[22]

In contrast, DOR inactivation was associated with an increase in both body weight-normalized food intake and total energy expenditure and was associated with a significantly reduced ratio of weight gain to food consumed.[20] The greater energy expenditure in DOR knockout mice appears to be driven at least in part by activation of thermogenesis, as evidenced by an increased body surface temperature and up-regulation of thermogenesis-associated genes in brown adipose tissue.[20] No increase in locomotor activity was observed relative to wild-type mice. DOR inactivation in the high-fat diet model was also associated with reduced liver triglyceride levels and hepatic fat storage, elevated fatty acid turnover in white adipose tissue, and decreased plasma triglyceride and leptin levels.[20] DOR deletion was protective against glucose
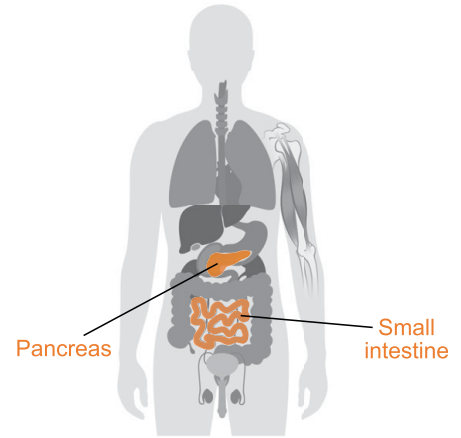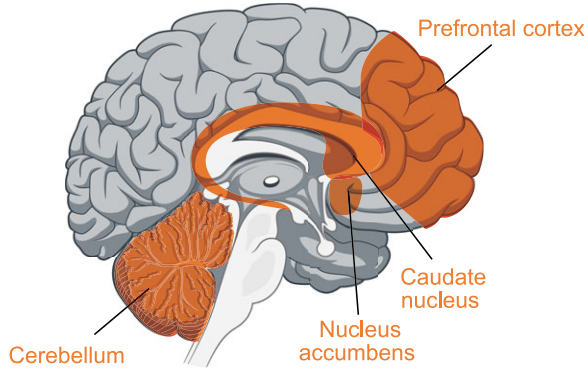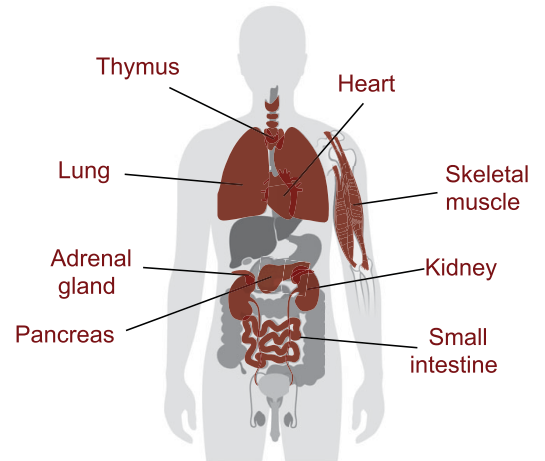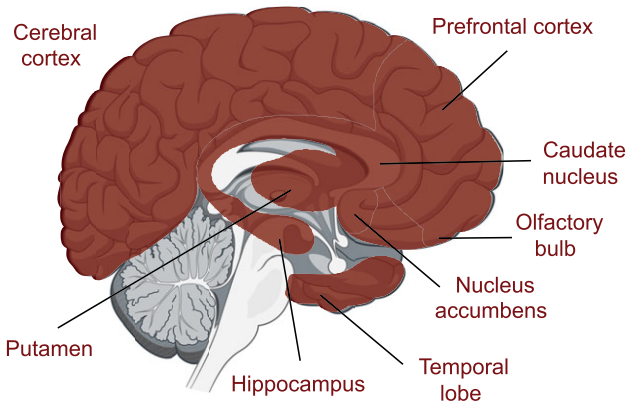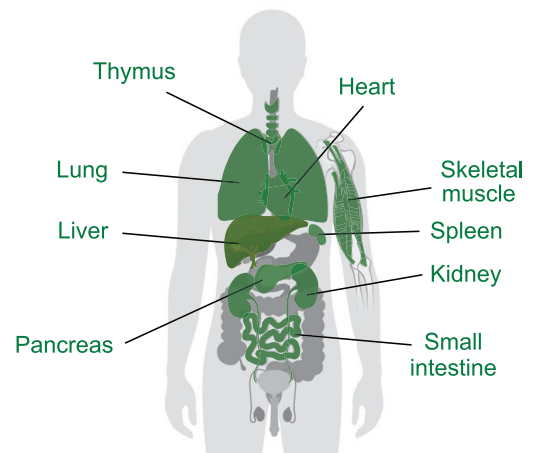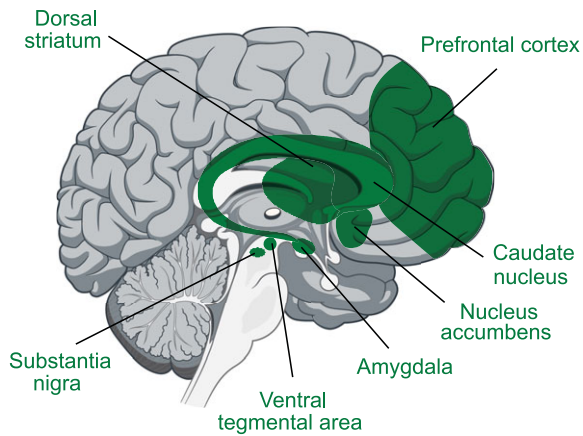
Figure 1. Distribution: areas of greatest expression of MOR, DOR, and KOR in the CNS and periphery.[24,29,50] Abbreviations: CNS, central nervous system; DOR, delta opioid receptor; KOR, kappa opioid receptor; MOR, mu opioid receptor. ©Alkermes, Inc. 2021.

Figure 2. Metabolism: effects of opioid receptor deletion in diet-induced obesity; murine knockout high-fat diet models.[19,20,22] Abbreviations: DOR, delta opioid receptor; KOR, kappa opioid receptor; MOR, mu opioid receptor. ©Alkermes, Inc. 2021.

intolerance in mice fed standard chow, and no difference was observed in body weight or adiposity relative to wild-type littermates.[20] Interestingly, this is in contrast with MOR knockout results, in which the protective effects on glucose intolerance were observed only in mice fed a high-fat diet.[22]

Standard diet-fed KOR knockout mice did not differ from wild-type mice in body weight, fat mass, food intake, or energy expenditure, yet these mice had significantly less fat-free mass.[19] KOR knockout mice fed a high-fat diet had reduced weight gain, fat mass, and fat-free mass, despite an increase in food intake and no difference in the percentage of calories absorbed vs excreted.[19] Unlike wild-type mice, which reduced energy expenditure when shifted from a standard to high-fat diet, mice lacking the KOR gene maintained their energy expenditure on a high-fat diet.[19] KOR knockout mice had elevated levels of spontaneous locomotor activity, but no evidence of increased thermogenesis in brown adipose tissue or skeletal muscle.[19] KOR inactivation was also associated with reduced lipid storage in liver and white adipose tissue, and increased fatty acid oxidation in the liver.[19]

Taken together, genetic deletion studies indicate that while MOR, DOR, and KOR each contribute to regulation of body weight, their specific roles differ regarding regulation of energy intake, storage, and utilization. Consequently, the effects of opioid receptor modulation may be expected to differ, depending on which opioid receptors are targeted, as well as the type of diet consumed.

Differential effects of opioid antagonists

Given the metabolic-related functions associated with the endogenous opioid system, drugs that interact with MOR, DOR, or KOR have the potential to produce effects on body weight and metabolism by regulating activity at those receptors. Whereas endogenous opioid receptor agonists bind to and activate receptors, opioid antagonists bind to and block receptor activation. While MOR, DOR, or KOR agonists each have been reported to stimulate food or caloric intake in rats[54] and humans,[55] administration of opioid antagonists conversely has been associated with attenuated food consumption and reduced fat accumulation in preclinical and clinical studies.[23,56-58]

Representative compounds that act as antagonists at MOR, DOR, and/or KOR identified in this focused review (eg, naltrexone, samidorphan, and LY255582) can be differentiated based on a number of characteristics, including ease of access to the systemic circulation and opioid receptors (pharmacokinetic profile), binding affinities, and/or the ability to inhibit agonist-induced activation of each receptor type.[59-61] Each of these properties could potentially impact their effects on regulation of body weight and metabolism, with distinctions between compounds observed both preclinically and clinically. Naltrexone is used in the treatment of patients with alcohol or opioid use disorder[62] and has been assessed in several other preclinical and clinical models.[63-73] In animal models of obesity, treatment with naltrexone has been associated with at least transient reductions in food intake and/or body weight gain.[69-72] Clinically, the effects of naltrexone on body weight or BMI have been reported in small studies enrolling overweight patients with polycystic ovary syndrome (PCOS),[66,67] binge eating,[68] or schizophrenia.[73] Samidorphan in combination with olanzapine (OLZ/SAM; Lybalvi, Alkermes, Inc.) is approved in the United States for the treatment of adults with schizophrenia or bipolar I disorder, including acute treatment of manic or mixed episodes as monotherapy and as an adjunct to lithium or valproate,

or as maintenance monotherapy treatment.[74] In clinical studies, OLZ/SAM treatment mitigated olanzapine-associated weight gain while maintaining antipsychotic efficacy.[23,75] LY255582 has been associated with reduced weight gain vs vehicle-treated controls in animal models of genetic and diet-induced obesity[49,57,59,70]; however, to the best of our knowledge, no data from human studies have been reported.

Pharmacokinetic parameters related to how much and the rate at which a drug is absorbed after oral administration (bioavailability; C_{max}), the time taken to reach maximum plasma concentration (T_{max}) after dosing, and how long effective plasma drug concentrations persist (half-life) are of interest for understanding a drug's clinical potential. The pharmacokinetics of naltrexone and samidorphan have been assessed in human studies[76,77]; the pharmacokinetics of LY255582 have been examined in animal models (rat and dog).[78] The reported oral bioavailability of naltrexone is variable, with estimates ranging from 5% to 40% (Table 1).[62,76] The bioavailability of samidorphan is 69%,[77] whereas for LY255582, it is <1% (in dogs).[78] The half-life of samidorphan (7-9 hours[77]; Table 1) is approximately twice as long as the half-lives of naltrexone and LY255582 (4 hours[62] and 3.2 hours,[78] respectively). Pharmacokinetic parameters such as these are of interest because a larger fraction of administered drug available to systemic circulation and greater persistence of that drug in circulating plasma increase the window for any clinically relevant receptor interactions.

Naltrexone, samidorphan, and LY255582 have distinct binding affinities at MOR, DOR, and KOR and also differ in their ability to block activation of those receptors in an assay measuring functional effects[79] (Table 2). Naltrexone binds with subnanomolar affinity at MOR ($K_i = 0.11$ nM) and KOR ($K_i = 0.19$ nM), but has much lower affinity for DOR ($K_i = 60$ nM).[80-82] Samidorphan has higher affinity for each of the 3 opioid receptors compared with naltrexone (MOR: $K_i = 0.052$ nM; DOR: $K_i = 2.6$ nM; KOR: $K_i = 0.23$ nM),[61,80,82] and LY255582 is a pan-opioid antagonist with a modest degree of selectivity for MOR ($K_i = 0.41$ nM) over DOR and KOR ($K_i = 5.2$ nM and $K_i = 2.0$ nM, respectively).[83] In the functional assay, both naltrexone and samidorphan are antagonists at MOR (>90% maximal inhibition of agonist-stimulated receptor activation) and mixed agonists/antagonists at DOR and KOR, stimulating or inhibiting opioid receptor activation under different conditions (Table 2).[61,79,84] However, at clinically relevant concentrations, samidorphan likely functions as an antagonist at both MOR and DOR, while naltrexone likely functions as an MOR antagonist.[56] LY255582 is a pan-opioid antagonist at MOR, DOR, and KOR[85] (Table 2); however, LY255582 has not been characterized

Table 1. Opioid Antagonist Pharmacokinetic Profiles: Naltrexone,[62,80] Samidorphan,[77] and LY255582[78]

Parameter	Naltrexone	Samidorphan	LY255582
C_{max}	8.6 ng/mL	≈25 ng/mL	11.5 ng/mL
T_{max}	1 h	1-2 h	0.6 h
$t_{1/2}$	4 h	7-9 h	3.2 h
Oral bioavailability	5%-40%	69%	<1%
Volume of distribution	1350 L	341 L	7.2 L/kg
Systemic clearance	3.5 L/min	33.7 L/h	1.6 L/h/kg
Excreted unchanged	<2%	19%	None

Abbreviations: C_{max}, maximum plasma concentration; $t_{1/2}$, terminal elimination half-life; T_{max}, time to maximum plasma concentration.

Table 2. Opioid Antagonist Receptor Binding and Functional Activity: Naltrexone,[60,79,80] Samidorphan,[79,80] and LY255582[59,60,83,85]

Receptor	Parameter[a]	Naltrexone	Samidorphan	LY255582
MOR	Receptor-binding affinity, K_i (nM)	0.11 (0.006)	0.052 (0.004)	0.41 (0.09)
	Stimulation of opioid receptor activation[b]			
	EC_{50} (nM)	16 (8.6)	NA	–
	E_{max} (%)	14 (0.82)	3.8 (0.67)	–
	Inhibition of agonist-stimulated opioid receptor activation[b]			
	IC_{50} (nM)	4.8 (0.42)	0.88 (0.14)	–
	I_{max} (%)	93 (0.87)	92 (2.9)	–
	K_e (nM)	3.35 (0.95)	–	0.10 (0.04)
DOR	Receptor-binding affinity, K_i (nM)	60 (3.2)	2.6 (0.26)	5.2[c]
	Stimulation of opioid receptor activation[b]			
	EC_{50} (nM)	21 (6.7)	1.8 (0.5)	18.3 (3.1)
	E_{max} (%)	14 (4.3)	35 (4.2)	–
	Inhibition of agonist-stimulated opioid receptor activation[b]			
	IC_{50} (nM)	130 (30)	6.9 (2.1)	–
	I_{max} (%)	88 (1.5)	56 (3.0)	–
	K_e (nM)	60.7 (10.6)	–	0.60 (0.11)
KOR	Receptor-binding affinity, K_i (nM)	0.19 (0.005)	0.23 (0.018)	2.02 (0.46)
	Stimulation of opioid receptor activation[b]			
	EC_{50} (nM)	3.3 (0.52)	3.3 (1.2)	–
	E_{max} (%)	3.9 (2.4)	36 (0.98)	–
	Inhibition of agonist-stimulated opioid receptor activation[b]			
	IC_{50} (nM)	130 (15)	38 (8.8)	–
	I_{max} (%)	54 (0.90)	57 (0.71)	–
	K_e (nM)	4.63 (1.49)	–	0.29 (0.06)

Abbreviations: CHO, Chinese hamster ovary; DAMGO, (D-Ala[2],MePhe[4],Gly-ol[5])enkephalin; DOR, delta opioid receptor; DPDPE, cyclo(D-Pen[2],D-Pen[5])enkephalin; E_{max}, maximal effect when all receptors are occupied by drug; EC_{50}, half-maximal effective concentration; I_{max}, maximal inhibition; IC_{50}, concentration of drug producing 50% inhibition; K_e, functional inhibition constant; K_i, inhibitory constant; KOR, kappa opioid receptor; MOR, mu opioid receptor; SEM, standard error of the mean.
[a]Values for each parameter are mean (SEM) from at least 3 experiments performed in triplicate.
[b]Receptor activation was assessed using a [^{35}S]GTPγS binding assay. Membrane protein from CHO cells that stably expressed one type of the human opioid receptor were incubated with the compound in the presence of either [^{3}H]DAMGO (MOR), [^{3}H]naltrindole or DPDPE (DOR), or [^{3}H]U69,593 (KOR).
[c]SEM not reported.

(or published, to the best of our knowledge) using the same assays reported here for naltrexone or samidorphan.

Because these opioid antagonists differentially bind to and inhibit activation of MOR, DOR, and KOR, and the specific effects of MOR, DOR, and KOR gene deletions on regulation of body weight and metabolism also differ, it is reasonable to expect that the preclinical and clinical effects of the individual opioid antagonists might differ as well. Differential effects of naltrexone, samidorphan, and LY255582 on body weight and metabolism observed in preclinical and clinical studies (Table 3) are summarized below. Preclinical and clinical data related specifically to olanzapine-associated weight gain are also highlighted.

Naltrexone

Naltrexone is used as a treatment in patients with alcohol or opioid use disorder.[62,86] Naltrexone in combination with bupropion is approved for chronic weight management in overweight or obese adults as an adjunct to a reduced-calorie diet and increased physical activity.[87] However, it should be noted that in clinical studies, naltrexone monotherapy has not been found to reduce weight in patients who are overweight or obese.[64,88]

In animal models, naltrexone reduces weight but not food intake in genetically obese mice and rats,[69,70] and decreases weight, fat mass, and caloric intake in rats fed a high-fat or sucrose-supplemented diet.[57,71,72] In mice fed a high-fat diet, transient effects on weight and food intake were reported.[72] Naltrexone's effects on antipsychotic-induced weight gain in rodents have been equivocal (Table 3). Assessed in a standard rodent model using female rats, naltrexone did not mitigate olanzapine-associated weight gain in 1 study,[89] but did reduce body weight gain and food intake in a second study.[58] Naltrexone had no effect on weight gain associated with the antipsychotic sulpiride in rats.[90]

Reductions in body weight have been observed with naltrexone in several small clinical studies for different conditions associated with weight gain, for example, in PCOS,[66,67] binge eating,[68] and in patients taking antipsychotics for schizophrenia.[73] In overweight or obese females with PCOS, naltrexone was associated with a reduction in BMI and with improvement in fasting insulin levels

Table 3. Summary of Studies Examining the Effects of Opioid Antagonists on Weight, Metabolism, and Appetite: Naltrexone, Samidorphan, and LY255582

Effect	Model	Naltrexone	Samidorphan	LY255582
Decrease in body weight/BMI				
Rodent				
Genetically obese[59,69,70]		☑		☑
Diet-induced obesity[49,57,71,72]		☒[a] ☑		☑
Normal weight[96]				☑
Rat, + sulpiride vs sulpiride alone[90]		☒		
Rat, + OLZ vs OLZ alone[56,58]		☒ ☑	☑	
Nonhuman primate				
Cynomolgus macaque + OLZ[56]			☑	
Human				
Overweight or obese females with PCOS[66,67]		☑		
Females with binge eating and type 1 diabetes[68]		☑		
Healthy volunteers, + OLZ vs OLZ alone[92]			☑	
Overweight females taking antipsychotics (diabetes group)[73]		☑		
Patients with schizophrenia, + OLZ vs OLZ alone[23,91,93]		☒	☑	
Decrease in fat mass/accretion/waist circumference				
Rodent				
Genetically obese[59]				☑
Diet-induced obesity[49,71]		☑		☑
Rat, + OLZ vs OLZ alone[56]			☑	
Nonhuman primate				
Cynomolgus macaque, + OLZ vs OLZ alone[b,56]			☑	
Human				
Overweight patients taking antipsychotics[73]		☒		
Patients with schizophrenia, + OLZ vs OLZ alone[23,91]		☑	☑	
Decrease in food intake				
Rodent				
Genetically obese[59,70]		☒		☑
Diet-induced obesity[49,57,72]		☒[a] ☑		☑
Normal weight[96]				☑
Rat, + sulpiride vs sulpiride alone[90]		☑		
Rat, + OLZ vs OLZ alone[56,58]		☑	☒	
Nonhuman primate				
Cynomolgus macaque, + OLZ vs OLZ alone[56]			☑	
Increase in insulin sensitivity				
Rodent				
Rat, + OLZ vs OLZ alone[56]			☒	
Nonhuman primate				
Cynomolgus macaque, + OLZ vs OLZ alone[b,56]			☑	
Decrease in serum insulin				
Rodent				
Genetically obese[59]				☒
Diet-induced obesity[49,57]				☑

Table 3. *Continued*

Effect	Model	Naltrexone	Samidorphan	LY255582
Human				
PCOS, overweight or obese[66,67]		☑		
Healthy volunteers, + OLZ vs OLZ alone[92]			☒	
Overweight patients taking antipsychotics[73]		☒		
Patients with schizophrenia, + OLZ vs OLZ alone[23,93]			☒	
Decrease in serum glucose				
Rodent				
Genetically obese[59]				☒
Diet-induced obesity[49,57]				☒☑
Human				
PCOS with low glucose:insulin[66]		☒		
Healthy volunteers, + OLZ vs OLZ alone[92]			☒	
Overweight patients taking antipsychotics[73]		☒		
Patients with schizophrenia, + OLZ vs OLZ alone[23,93]			☒	
Decrease in triglycerides				
Rodent				
Genetically obese[59]				☒
Diet-induced obesity[57]				☑
Human				
Healthy volunteers, + OLZ vs OLZ alone[92]			☒	
Overweight patients taking antipsychotics[73]		☒		
Patients with schizophrenia, + OLZ vs OLZ alone[23,91,93]		☒	☒	
Decrease in total cholesterol				
Rodent				
Genetically obese[59]				☒
Diet-induced obesity[57]				☑
Human				
Healthy volunteers, + OLZ vs OLZ alone[92]			☑	
Overweight patients taking antipsychotics[73]		☒		
Patients with schizophrenia, + OLZ vs OLZ alone[23,91,93]		☒	☒	

Notes: ☑ reported effect; ☒ no reported effect; cells with no symbol shown indicate that the measure was not assessed.
Abbreviations: BMI, body mass index; OLZ, olanzapine; PCOS, polycystic ovary syndrome.
[a]Transient effect only.
[b]Not tested statistically.

in 1 small study (N = 30),[66] and with weight loss, reduced BMI, and reduced insulin levels, particularly in females with low baseline glucose:insulin ratios, in a second study (N = 10).[67] Females with binge eating and type 1 diabetes treated with naltrexone (N = 3) had reductions in body weight and binging episodes, and improvement in hemoglobin A_{1c} levels.[68]

The reported effects of naltrexone on antipsychotic-induced weight gain have also varied in clinical studies (Tables 3 and 4). In a pilot study of overweight females with schizophrenia or schizoaffective disorder who were taking antipsychotic medication at enrollment (N = 24), naltrexone treatment was associated with weight loss vs placebo over 8 weeks.[73] Of note, based on a subgroup analysis, weight loss was observed only in non-diabetic (n = 5) patients; no weight loss was observed in patients with diabetes (n = 6).[73] There were no significant changes in waist circumference or metabolic parameters observed.[73] In a second study enrolling obese or overweight patients on a stable dose of olanzapine for the treatment of schizophrenia or schizoaffective disorder (N = 30), there were no significant changes in body weight or BMI from baseline to week 12 in either naltrexone or placebo groups, although a significant reduction in fat mass and fat-free mass was observed at week 12 with naltrexone.[91] No differences in lipids were observed between treatment groups.[91]

Samidorphan

The effects of samidorphan (previously referred to as ALKS 33 and as RDC-0313) on body weight and metabolic parameters have focused on animal and human studies of olanzapine-associated weight gain[23,56,92,93] (Table 3); based on preclinical and clinical observations, samidorphan monotherapy would not be expected to result in weight loss.[56,92] In preclinical studies, samidorphan attenuated olanzapine-associated increases in weight and adiposity in both rats and nonhuman primates.[56] A transient decrease in food intake was observed in rats after treatment with olanzapine plus samidorphan.[56] Olanzapine administered alone decreased hepatic insulin sensitivity and glucose utilization in muscle while increasing glucose utilization in adipose tissue. Samidorphan attenuated the olanzapine-associated effects on glucose utilization but did not restore hepatic insulin sensitivity.[56] In nonhuman primates fed a high-fat diet, food intake was reduced after treatment with olanzapine plus samidorphan vs olanzapine.[56] Olanzapine treatment was associated with a decrease in insulin sensitivity in monkeys, which was prevented by coadministration of samidorphan.[56]

In humans, samidorphan mitigated olanzapine-associated weight gain in both healthy volunteers[92] and in patients with schizophrenia in phase 2 and phase 3 clinical studies (Table 4).[23,93,94] Increased waist circumference, which has been associated with greater risk of cardiovascular disease and diabetes,[95] was also attenuated in patients treated with OLZ/SAM compared with patients treated with olanzapine in a phase 3 study.[23] Changes from baseline in mean serum insulin, glucose, or triglyceride levels were similar after treatment with olanzapine plus samidorphan vs olanzapine in healthy subjects[92] and in patients with schizophrenia[93]; levels were also similar after 24-week treatment with OLZ/SAM vs olanzapine in patients with schizophrenia.[23] Treatment with olanzapine in combination with samidorphan was associated with a smaller increase in total cholesterol levels compared with olanzapine in healthy subjects[92]; however, no difference in total cholesterol levels was observed after treatment with OLZ/SAM vs olanzapine in patients with schizophrenia.[23]

LY255582

To date, LY255582 has not been assessed in human or animal studies assessing effects on antipsychotic-associated weight gain, but it has been examined in animal models of obesity[49,57,59,70] (Table 3). In genetically obese rats[59,70] and in rats with diet-induced obesity,[49,57] LY255582 reduced food intake, body weight gain, and fat mass; LY255582 also reduced body weight and food intake in normal weight rats.[96] No significant differences were observed between LY255582 and vehicle control groups in glucose, triglycerides, total cholesterol, or insulin after 68 days of treatment in genetically obese rats.[59] LY255582 reduced insulin levels compared with the vehicle control in rats with diet-related obesity[49,57]; glucose levels were unchanged vs control on day 11,[49] but significantly reduced after 4 weeks of treatment.[57] LY255582 in rats fed a high-

Table 4. Clinical Studies Assessing Opioid Antagonist Mitigation of Antipsychotic-Associated Weight Gain

Reference	Opioid antagonist	N	Study population	Study design	Primary outcome
Tek et al[73]	Naltrexone	24	Female patients aged 18-70 y with schizophrenia or schizoaffective disorder, BMI ≥27 kg/m², weight gain in the last year (≥2% over previous year's weight), and on a stable dose of antipsychotic medication	8-wk, randomized, double-blind, placebo-controlled pilot study	Change in body weight from baseline to week 8
Taveira et al[91]	Naltrexone	30	Patients aged 21-55 y with schizophrenia or schizoaffective disorder, BMI ≥30 kg/m² (or ≥27 kg/m² with ≥1 symptom of metabolic syndrome) at screening, and stable dose of olanzapine (≥2 mo)	12-wk, randomized, double-blind, placebo-controlled pilot study	Change in BMI from baseline to week 12
Silverman et al[92]	Samidorphan	106	Male volunteers aged 18-40 y with BMI of 18-25 kg/m² at screening, and stable body weight over previous ≥3 mo	3-wk randomized, double-blind, double-dummy, placebo- and active-controlled study	Absolute change in body weight from baseline to week 3
Martin et al[93]	Samidorphan	309	Patients aged 18-50 y with schizophrenia, BMI of 17-30 kg/m² at screening, and stable body weight for ≥3 mo prior to screening	12-wk, phase 2, randomized, double-blind, placebo-controlled, safety, tolerability, and dose-ranging study; 12-wk open-label extension	Absolute change in PANSS total score from baseline to week 12 (secondary: percent change in body weight and proportion of patients with ≥7% and ≥10% weight gain from baseline to week 12)
Correll et al[23]	Samidorphan	550	Patients aged 18-55 y with schizophrenia, BMI of 18-30 kg/m² at baseline, and stable body weight for ≥3 mo prior to study initiation	24-wk, phase 3, randomized, double-blind study	Percent change in body weight from baseline at week 24, and proportion of patients with ≥10% weight gain from baseline at week 24 (secondary: proportion of patients with ≥7% weight gain from baseline at week 24)

Abbreviations: BMI, body mass index; PANSS, Positive and Negative Syndrome Scale.

fat diet was also associated with significant improvement in lipid profile[57] and with changes in energy utilization (a shift from fat to carbohydrate utilization).[49]

Discussion

This review summarizes the potential role of the opioid system in regulating metabolic sequelae, including weight, as well as a potential role in antipsychotic-associated weight gain and metabolic dysregulation. While the published data for naltrexone, samidorphan, and LY255582 support a role for the endogenous opioid system in the regulation of metabolism and weight, they also suggest that the specific effects of opioid antagonists on weight gain, fat mass accumulation, food intake, and regulation of energy utilization vary, likely owing to differential pharmacokinetic, binding, and functional activity profiles. However, animal models and clinical studies indicate that opioid antagonism can be employed to mitigate the adverse effects of antipsychotics on metabolic function.

The data summarized here are from analyses that did not directly compare these 3 compounds, and given the noted heterogeneity among opioid antagonists, generalizations to other opioid antagonists cannot be made. Observed effects on antipsychotic-associated weight gain and metabolic dysregulation vary among the opioid antagonists examined, and are likely due to their differing pharmacokinetics and pharmacodynamic profiles at MOR, DOR, and KOR. Results from preclinical and clinical studies with these representative molecules illustrate that opioid receptor antagonism can modify metabolic regulation, while also suggesting that unique characteristics of individual opioid antagonists may result in different clinical effects in terms of their ability to mitigate weight gain and metabolic sequelae. Additionally, these findings are based on limited evidence obtained from the published literature, which may have been skewed by publication bias; we were unable to locate results of any clinical study for LY255582.

Conclusions

Preclinical and clinical data suggest that the endogenous opioid system is involved in regulating aspects of metabolism, including weight regulation, and that the opioid system is a viable target to address antipsychotic-associated weight gain and metabolic dysregulation. Antipsychotic-associated weight gain can reduce patients' quality of life and satisfaction with care, and may negatively impact treatment adherence.[97,98] Opioid receptor antagonism may be a strategy to mitigate/limit the weight and metabolic-related effects, and its use could thereby increase the clinical utility of otherwise highly efficacious pharmacologic treatments that are associated with weight gain. Differences in observed preclinical and clinical weight-related effects of 3 opioid receptor antagonists, each with distinct pharmacokinetic characteristics, binding, and functional activity profiles with respect to MOR, DOR, and KOR, underscore that the unique properties of individual opioid receptor antagonists may yield important differences in their effectiveness for mitigating antipsychotic-associated weight gain.

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