QSPainRelief

Effective combinational treatment of chronic pain in individual patients, by an innovative quantitative systems pharmacology pain relief approach.

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Author List

Organisation	Name	Contact information
CHDR	Wouter Bakker	WBakker@chdr.nl
CHDR	Geert Jan Groeneveld	ggroeneveld@chdr.nl
ULEI	Liesbeth de Lange	ecmdelange@lacdr.leidenuniv.nl
concentris	Nina Donner	nina.donner@concentris.de

Abbreviations

5-HT	serotonin (5-hydroxy-tryptamin)
5-HT1A/2A	serotonin receptor 1A / 2A
5-HT1B/1D	serotonin receptor 1B / 1D
5-HT4	serotonin receptor 4
α2	alpha-2 adrenergic receptor
CHDR	Centre for Human Drug Research
COMT	catechol-O-methyltransferase
concentris	concentris research management gmbh
CNS	central nervous system
CTZ	chemoreceptor trigger zone
CUI	clinical utility index
CYP	cytochrome P450
D2	dopamine receptor 2
ECF	extracellular fluid
MAO-A	Monoamine Oxidase A
OIH	opioid-induced hyperalgesia
QSP	Quantitative Systems Pharmacology
UGT2B7	UDP-Glucuronosyltransferase-2B7
ULEI	Universiteit Leiden

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1. Executive summary

The objective of this report is to present the effectiveness of 34 augmentation drugs combined with four different doses of morphine, as expressed by a Clinical Utility Index (CUI) for each combination. The report lists the ten combinations with the lowest CUI scores and summarizes potential reasons for their limited or absent additive analgesic effects, as supported by relevant literature. Brain extracellular fluid concentrations of morphine and augmentation drugs were predicted using the LeiCNS-PK model as part of the QSPainRelief model platform. These concentrations were then used in the LeiCNS-BK model to estimate target occupancy at relevant receptors and transporters. The resulting values served as input for QSPainRelief models to simulate analgesic, sedative, cognitive, and abuse liability effects. Five key factors potentially contributing to the lack of additive analgesic effects found in the LeiCNS-KP model are outlined in this report, including pharmacodynamic interactions and adverse effects. While some combinations may theoretically enhance analgesia, they often result in increased toxicity and safety concerns. The findings align with existing literature, but further validation is needed to confirm the model's predictive accuracy regarding synergistic effects. This report is a valuable resource for clinicians and researchers aiming to improve pain management strategies.

2. Deliverable report

Methods

This Delivery Report highlights the 10 least favourable combos of 34 augmentation drugs at three different doses in combination with four different doses of morphine (15 mg, 30 mg, 45 mg and 60 mg) (Table 1). Previously, in Delivery Report D2.12, predictions based on the LeiCNS-PK model as part of the QSPainRelief model platform were given for the effects of the 34 augmentation drugs in combination with morphine. Predictions involved the following steps for each drug combination:

(1) The LeiCNS-PK model was used to determine the brain extracellular fluid (ECF) concentrations for the four different doses of morphine (based on taking a third of the daily total every 8 hours with the PK constants describing a case between instant release and extended release. Further details about the model can be found in Delivery Report D2.12.

(2) Drug brain ECF concentration were used to as input for the LeiCNS-PK model to determine the target engagements for mu-opioid receptors with morphine, and for serotonergic, dopaminergic, noradrenergic and muscarinic receptors and transporters with the augmentation drug, resulting in specific target occupancy values.

(3) The target occupancy values were used as input for the QSPainRelief neuronal circuit models and analgesic, sedative, cognitive, and abuse liability effects were simulated.

Results

Ranking of drug combinations

In order to take into account all simulated effects (analgesia, drug abuse liability, cognitive impairment and sedation), a clinical utility index (CUI) was calculated for each combination of augmentation drugs. For each of the above-mentioned effect, we normalized the effects through a linear transformation so that the minimum response is zero, maximum response is one and the minimal response is minus one. For all CUIs per simulated effect, we refer to Delivery Report D2.12. The combinations were rank ordered for each effect and overall normalized CUIs were calculated based on the minimum and maximum values over all morphine doses. This Delivery Report highlights the 10 least favourable combinations, as presented in Table 2 and reflects on the reasons for lack of additive analgesic effects.

Overall, metoclopramide showed the least favourable response ranking when combined with both high (the average of 15 mg and 30 mg doses) and low (the average of 45 mg and 60 mg doses) dosed morphine. Other combinations with low CUIs are bupropion, buspirone, clonidine, yohimbine, sumatriptan, tolcapone and doxepin, combined with a high dose of morphine. Clonidine combined with low dosed morphine was also referred to as low response combination.

Interestingly, 8 out of the 10 low response combinations included high dosed morphine, highlighting the side effect problems associated with opioids, especially at greater doses. However, metoclopramide and clonidine also showed a low response when combined with low doses of morphine.

Key factors contributing to limited additive analgesic effects

When morphine is involved in a drug combination but fails to show (additive) analgesic effects, or leads to a serious increase in severity of adverse effects, several key factors could be at play, summarized into 5 main reasons:

1. *Pharmacodynamic Agonism.* Overlapping mechanisms of action: Some drugs may compete for the same receptors or excessively activate receptors. For example, another opioid with partial agonist activity (e.g., buprenorphine) in combination with morphine, may compete for the same mu-opioid receptors, which might not activate the receptor as strongly as morphine, leading to submaximal analgesic effects. Conversely if another full agonist (e.g., fentanyl) is used alongside morphine, there can be an excessive activation of opioid receptors, leading to an increase in side effects.

2. *Pharmacodynamic Antagonism*. Opposing mechanisms of action: Some drugs may counteract morphine's effects. For example, naloxone (an opioid antagonist) directly blocks morphine's action at the μ-opioid receptor. Tolerance development: Chronic morphine use leads to receptor desensitization, reducing the efficacy of co-administered drugs that rely on opioid receptor activation.

3. *Pharmacokinetic Interactions*. Metabolism interference: Morphine is primarily metabolized by UDP-Glucuronosyltransferase-2B7 (UGT2B7) into active and inactive metabolites. If a co-administered drug alters UGT2B7 activity, it can change morphine's analgesic effect. Enzyme induction or inhibition: Drugs that induce hepatic enzymes (e.g., rifampin) can accelerate morphine clearance, reducing its efficacy. Conversely, enzyme inhibitors (e.g., valproate) may prolong morphine's effects, but not necessarily in a beneficial way.

4. *Receptor Cross-Talk and Adaptation*. Opioid-induced hyperalgesia (OIH): Long-term opioid exposure can paradoxically increase pain sensitivity, making certain drug combinations less effective. Dopaminergic and GABAergic interactions: Morphine affects dopamine signalling, so co-administration with drugs acting on these pathways (e.g., certain antipsychotics) can lead to unpredictable or diminished effects.

5. *Adverse effects.* Even if two drugs theoretically provide complementary therapeutic effects, excessive toxicity, overlapping side effects, and life-threatening risks can make the combination unsafe and non-synergistic. A successful drug pairing must maximize efficacy while keeping toxicity within acceptable limits. Additive or synergistic toxicity is defined by two drugs target different mechanisms; their combined toxicity can outweigh any potential benefit.

In this discussion, we reflect the reasons for lack of (additive) analgesic effects for each combination, underpinned by relevant literature. Consequently, we rate the reasons as either applicable or not applicable. Table 3 summarizes our findings.

METOCLOPRAMIDE AND MORPHINE

Pharmacodynamic Agonism. Both metoclopramide and morphine can cause enhanced central nervous system (CNS) depression, increasing the severity of adverse events such as sedation, drowsiness, dizziness or respiratory depression. A clinical trial comparing the effects of cisapride and metoclopramide on morphine-induced gastric emptying delays also reported increased sedation in patients receiving both morphine and metoclopramide.[1] While the study primarily focused on gastrointestinal motility, the enhanced CNS depression observed suggests a potential pharmacodynamic agonism between the two drugs. Metoclopramide, as a dopamine receptor (D2) antagonist, may potentiate morphine's sedative effects through indirect modulation of neurotransmission in the CNS.

Pharmacodynamic Antagonism. Metoclopramide is a D2 receptor antagonist with prokinetic and antiemetic effects. Its mechanism of action involves inhibition of dopaminergic signalling in the chemoreceptor trigger zone (CTZ)**,** reducing emetic responses, while also enhancing cholinergic activity in the gastrointestinal tract, leading to increased gastric motility and accelerated gastric emptying. By diminishing gastrointestinal motility, morphine may antagonize the pharmacologic effects of gastrointestinal prokinetic agents such as metoclopramide. However, it does not directly block morphine's primary action, so antagonism is mild. A clinical trial investigating the effect of intravenous metoclopramide on morphine-induced gastric emptying delays demonstrated a clear pharmacodynamic antagonism between the two drugs.[2] Morphine significantly slowed gastric emptying, as measured by paracetamol absorption, but this effect was effectively reversed by intravenous metoclopramide, whereas intramuscular administration showed no such benefit. This suggests that metoclopramide, through its prokinetic action via 5-hydroxy-tryptamin (serotonin) receptor 4 (5-HT4) agonism and D2 antagonism, counteracts opioid-induced gastrointestinal stasis.

Pharmacokinetic Interactions. Likely minimal, as metoclopramide does not significantly affect the metabolism of morphine.

Receptor Cross-Talk and Adaptation. There is no significant receptor cross-talk in this combination. Metoclopramide's actions are mainly on the dopamine system, while morphine acts on opioid receptors.

Adverse Events. Concomitant use of metoclopramide may increase CNS effects such as sedation, dizziness, confusion, and mental depression

Summary. Unless morphine and metoclopramide affect different receptor systems (opioid vs. dopamine), they influence each other's signalling pathways. Reasons for the lack of synergy between metoclopramide and morphine could be primarily adverse effects, pharmacodynamic agonism and slight pharmacodynamic antagonism.

BUPROPION AND MORPHINE

Pharmacodynamic Agonism. Bupropion is a dopamine-norepinephrine reuptake inhibitor. The interaction between bupropion and morphine does not primarily involve pharmacodynamic agonism.

Pharmacodynamic Antagonism. Bupropion does not directly oppose morphine's analgesic effects, though it may have some influence on CNS activity.

Pharmacokinetic Interactions. Bupropion affects cytochrome P450 enzymes (e.g., CYP2B6), which may alter morphine's metabolism to a small extent, though this is not a major interaction.

Receptor Cross-Talk and Adaptation. The combination could lead to alterations in dopamine signalling, but no strong receptor cross-talk occurs.

Adverse effects. Bupropion has a seizure risk at higher doses, and combining it with morphine could increase sedation, which could lead to additive or synergistic toxicity if not monitored carefully.[3,4 5]

Summary. Unless bupropion does not directly oppose morphine's analgesic effects by being a dopamine-norepinephrine reuptake inhibitor, it's mechanism may have an influence on CNS activity. Bupropion has a seizure risk at higher doses, and combining it with morphine could increase sedation, which could lead to additive or synergistic toxicity if not monitored carefully. Reasons for the lack of synergy between bupropion and morphine could be primarily considered adverse effects and slight pharmacodynamic and pharmacokinetic antagonism.

BUSPIRONE AND MORPHINE

Pharmacodynamic Agonism. Buspirone is a serotonin receptor 1A (5-HT1A) agonist and has mild anxiolytic effects. Buspirone does not exhibit pharmacodynamic agonism with morphine in producing antinociception, but both drugs act on the CNS and could lead to sedation.[6,7]

Pharmacodynamic Antagonism. Buspirone does not directly oppose morphine's mechanism of action.

Pharmacokinetic Interactions. Minimal, as buspirone does not significantly interfere with morphine metabolism.

Receptor Cross-Talk and Adaptation. Buspirone's serotonergic activity could interact with morphine's effects on the brain's pain and reward pathways.

Adverse Effects. Combining buspirone with morphine could lead to increased sedation or CNS depression.

Summary. Because of additive CNS depression, buspirone should generally be avoided in combination with morphine. Buspirone does not directly oppose morphine's action, but both drugs act on the CNS and its combination could lead to extra sedation. Reasons for the lack of synergy between buspirone and morphine could be primarily considered adverse effects and pharmacodynamic agonism.

CLONIDINE AND MORPHINE

Pharmacodynamic Agonism. Clonidine is an α2-adrenergic receptor agonist and can reduce sympathetic outflow. Co-administration of morphine and clonidine is known to result in synergistic antinociceptive effects without a corresponding increase in sedative, motor, or cardiovascular side effects.[89]

Pharmacodynamic Antagonism. Clonidine may potentiate morphine's analgesic effects by inhibiting norepinephrine release, leading to possible synergistic effects, not antagonism.

Pharmacokinetic Interactions. Minimal interactions as clonidine does not affect morphine metabolism.

Receptor Cross-Talk and Adaptation. Both clonidine and morphine affect the CNS, with clonidine enhancing analgesia through its α2-adrenergic effect, which could potentially amplify morphine's effects.

Adverse Effects. Many psychotherapeutic and CNS-active agents, such as opioids, exhibit hypotensive effects, especially during initiation of therapy and dose escalation. Coadministration with antihypertensives and other hypotensive agents, in particular vasodilators and alpha-blockers, may result in additive effects on blood pressure and orthostasis. [10]

Summary. Combining clonidine with morphine could enhance sedation or hypotension, leading to additive toxicity if not carefully managed. Clonidine may potentiate morphine's analgesic effects, which could not be confirmed by the prediction model. Reasons for the lack of synergy between clonidine and morphine could be primarily considered adverse effects.

YOHIMBINE AND MORPHINE

Pharmacodynamic Agonism. Based on its mechanisms of action, yohimbine—a selective α2-adrenergic antagonist — does not exhibit pharmacodynamic agonism with morphine.

Pharmacodynamic Antagonism. As an α2-adrenergic antagonist, yohimbine can increase norepinephrine release, leading to potential antagonism of morphine's effects. Conversely, a double-blind, placebo-controlled study in male patients with postoperative dental pain investigated the impact of preoperative administration of the α2-adrenergic antagonist yohimbine on postoperative intravenous morphine analgesia. While yohimbine alone had no effect on pain, it significantly enhanced the overall analgesic effect of morphine. These findings contradict the previously mentioned assumption that yohimbine would counteract morphine's effects.[9,11]

Pharmacokinetic Interactions. No significant effects on morphine's metabolism.

Receptor Cross-Talk and Adaptation. Yohimbine's effects on α2 receptors might oppose some of morphine's central effects.

Adverse Effects. Yohimbine's effects on α2 receptors might oppose some of morphine's CNS effects. The combination could cause an increase in heart rate, blood pressure, and anxiety, leading to adverse cardiovascular effects, potentially contributing to toxic interactions. In addition, there could also be a risk of CNS overstimulation, as yohimbine might interfere with the calming effects of morphine.

Summary. Combining yohimbine with morphine might oppose some of morphine's central effects, however evidence is not conclusive. The combination of yohimbine and morphine could cause an increase in heart rate, blood pressure and anxiety. Reasons for the lack of synergy between yohimbine and morphine could be primarily considered adverse effects and slight pharmacodynamic antagonism.

SUMATRIPTAN AND MORPHINE

Pharmacodynamic Agonism. Sumatriptan is a 5-HT1B/1D receptor agonist used for migraines. Sumatriptan and morphine have been associated with CNS depression. Co-administration may increase the risk or severity of CNS depressive effects, such as drowsiness or respiratory depression[6,7].

Pharmacodynamic Antagonism. Sumatriptan does not exhibit pharmacodynamic antagonism with morphine.

Pharmacokinetic Interactions. Sumatriptan is metabolized by MAO-A, but it does not significantly affect morphine's metabolism.

Receptor Cross-Talk and Adaptation. Sumatriptan affects serotonin pathways, which might interact with morphine's effects, although the interaction is mild.

Adverse Effects. Opioids may potentiate the effects of serotonergic agents like sumatriptan and increase the risk of serotonin syndrome. The interaction has primarily been reported with the phenylpiperidine opioids (e.g., meperidine, fentanyl) and tramadol, which are known to possess some serotonergic activity, although a few cases have involved other opioids such as oxycodone, methadone, morphine, hydromorphone, codeine, and buprenorphine. Serotonin syndrome is a rare but serious and potentially fatal condition thought to result from hyperstimulation of brainstem 5-HT1A and 2A receptors.

Summary. Sumatriptan affects serotonin pathways, which might interact with morphine's effects, although the interaction is mild. Combining sumatriptan with morphine could potentially increase the risk of serotonin syndrome, especially if other serotonergic drugs are involved. Reasons for the lack of synergy between sumatriptan and morphine could be primarily considered adverse effects and slight pharmacodynamic agonism.

TOLCAPONE AND MORPHINE

Pharmacodynamic Agonism. Tolcapone is a catechol-O-methyltransferase (COMT) inhibitor used in Parkinson's disease treatment. Overlapping effects of tolcapone and morphine on the dopaminergic system may lead to adverse outcomes, such as increased sedation or cognitive impairment, which are not necessarily additive but rather indicative of competing mechanisms that can exacerbate side effects. Thus, while both drugs may have therapeutic effects, their interaction could lead to antagonistic outcomes in terms of overall efficacy and safety.[12]

Pharmacodynamic Antagonism. Tolcapone does not directly oppose morphine's analgesic effects. However, it may influence dopamine signalling, potentially interacting with morphine's effects on the brain's reward system.

Pharmacokinetic Interactions. Tolcapone inhibits COMT, which might influence morphine metabolism by affecting the breakdown of certain metabolites.

Receptor Cross-Talk and Adaptation. Tolcapone could affect dopaminergic pathways, and morphine also interacts with the dopaminergic system, so there could be some receptor cross-talk.

Adverse Effects. There is a potential for additive or synergistic toxicity due to CNS effects (sedation, confusion), and liver function should be monitored due to tolcapone's hepatic metabolism.

Summary. During concomitant use of these drugs, patients should be monitored for potentially excessive or prolonged CNS and respiratory depression. Reasons for the lack of synergy between tolcapone and morphine could be primarily considered adverse effects and pharmacodynamic agonism and slight pharmacodynamic and pharmacokinetic antagonism, as well as receptor cross-talk.

DOXEPIN AND MORPHINE

Pharmacodynamic Agonism. Doxepin is a tricyclic antidepressant that can cause CNS depression and sedative effects. Concomitant use of doxepin and morphine may result in additive CNS depressive effects, increasing the risk of side effects [13].

Pharmacodynamic Antagonism. There is no direct antagonism of morphine's analgesic effects.

Pharmacokinetic Interactions. Doxepin is metabolized by CYP enzymes, which could potentially alter morphine metabolism, though this interaction is not usually significant.

Receptor Cross-Talk and Adaptation. Doxepin acts on serotonin and norepinephrine pathways, which could interact with morphine's analgesic effects and enhance sedative effects.

Adverse Events. Combining morphine with doxepin may increase the risk of CNS depression, leading to potentially hazardous levels of sedation and respiratory depression, making the combination potentially toxic.

Summary. Doxepin enhances morphine's sedative and CNS-depressant effects but does not directly antagonize its analgesia. While potential CYP-mediated pharmacokinetic interactions are minor, the combination may increase the risk of excessive sedation and respiratory depression due to receptor cross-talk and additive adverse effects by pharmacodynamic agonism.

Summary of findings

This report highlights various mechanisms through which co-administration can influence efficacy and safety. The drug combinations listed work via dopaminergic (metoclopramide, bupropion and tolcapone), serotonergic (buspirone, sumatriptan, doxepin) and adrenergic (clonidine and yohimbine) pathways. Overall, these pathways can either enhance or diminish the analgesic, sedative, cognitive, and abuse liability effects of opioids, depending on the specific interactions and the balance of neurotransmitter activity. Understanding these interactions is crucial for optimizing pain management strategies and minimizing side effects.

Dopaminergic Pathway: Opioids, such as morphine, increase dopamine release in the brain's reward system, enhancing analgesia and euphoria. Drugs like metoclopramide and can modulate this pathway. Metoclopramide may reduce the rewarding effects of opioids, potentially leading to decreased analgesic efficacy, while bupropion could enhance the overall dopaminergic activity, possibly improving pain relief.

Serotonergic Pathway: Opioids can also influence serotonin levels, which play a role in pain modulation. Buspirone and sumatriptan can interact with this pathway, potentially enhancing analgesic effects when combined with opioids. However, excessive serotonergic activity can lead to adverse effects, such as serotonin syndrome.

Adrenergic Pathway: Clonidine and yohimbine interact with the adrenergic system, which is involved in pain modulation and the stress response. Clonidine can enhance opioid analgesia by reducing sympathetic outflow and improving pain control, while yohimbine may counteract some of the analgesic effects of opioids by increasing norepinephrine release, potentially leading to increased pain sensitivity.

Table 3 indicates that adverse effects are a common concern across most combinations, while pharmacodynamic interactions vary, with some drugs exhibiting both agonistic and antagonistic properties that complicate their use alongside morphine.

3. Tables and other supporting documents

Table 1: Augmentation drugs dosed in combination with morphine

Drug	Dose1 (total)	Freq (/day)	Dose2 (total)	Freq (/day)	Dose3 (total)	Freq/ (/day)
amitriptyline	100 mg	2	75 mg	2	50 mg	2
aripiprazole	15 mg	1	10 mg	1	5 mg	2
atomoxetine	80 mg	1	60 mg	1	40 mg	1
brexpiprazole	4 mg	1	3 mg	1	2 mg	1
bupropion	300 mg	2	200 mg	2	100 mg	1
buspirone	60 mg	2	40 mg	2	20 mg	2
citalopram	40 mg	1	30 mg	1	20 mg	1
clomipramine	100 mg	1	75 mg	1	50 mg	1
clonidine	0,6 mg	2	0,4 mg	2	0,2 mg	2
desipramine	200 mg	1	150 mg	1	100 mg	1
desvenlafaxine	50 mg	1	37,5 mg	1	25 mg	1
doxepin	150 mg	1	100 mg	1	50 mg	1
duloxetine	60 mg	1	40 mg	1	20 mg	1
escitalopram	20 mg	1	15 mg	1	10 mg	1
fluoxetine	60 mg	2	40 mg	2	20 mg	2
fluvoxamine	300 mg	2	200 mg	2	100 mg	2
granisetron	2 mg	1	1.5 mg	1	1 mg	1
guanfacine	3 mg	1	2 mg	1	1 mg	1
imipramine	200 mg	1	150 mg	1	100 mg	1
lisuride	0,6 mg	1	0,4 mg	1	0,2 mg	1
maprotiline	150 mg	1	100 mg	1	50 mg	1
metoclopramide	60 mg	3	40 mg	4	20 mg	2
milnacipran	150 mg	2	100 mg	2	50 mg	2
nortriptyline	100 mg	4	75 mg	3	40 mg	4
paroxetine	40 mg	1	30 mg	1	20 mg	1
pramipexole	4,5 mg	3	3 mg	3	1,5 mg	3
reboxetine	12 mg	3	8 mg	1	4 mg	1
sertraline	200 mg	1	150 mg	1	100 mg	1
sumatriptan	100 mg	1	75 mg	1	50 mg	1
tolcapone	300 mg	3	200 mg	2	100 mg	1
trazodone	300 mg	3	200 mg	2	100 mg	2
venlafaxine	225 mg	1	150 mg	1	75 mg	1
vortioxetine	20 mg	1	15 mg	1	10 mg	1
yohimbine	15 mg	3	10 mg	2	5 mg	1

Table originated from Delivery Report D2.12. List of 34 augmentation drugs at three different total daily doses along with their daily frequency. For example, 15 mg with a frequency of 3 means that a 5 mg dose is taken every eight hours. These values were determined based on known daily dosages for the medications and were used to determine the brain concentrations in multiple compartments used in the neuronal models based on the PK modelling.

Table 2: Least favourable 10 combinations based on overall CUI

ranking in table 13	combination	morphine dose[1]	CUI[2]
68	metoclopramide	high	-0,66
67	metoclopramide	low	-0,57
66	bupropion	high	-0,47
65	buspirone	high	-0,44
64	clonidine	high	-0,42
63	yohimbine	high	-0,37
62	sumatriptan	high	-0,36
61	tolcapone	high	-0,32
60	doxepin	high	-0,27
59	clonidine	low	-0,22

[1] High: the average of 15 mg and 30 mg doses; low: the average of 45 mg and 60 mg doses.[2]CUI: clinical utility index. Table is based on Table 13 in Delivery Report D2.12.

Table 3: Reasons for lacking synergy of drug combinations

combination	morphine dose[1]	type	pharmacological pathway	reasons[2]				
				PD-AGO	PD-ANTA	PK	RC	AE
metoclopramide	high	dopamin antagonist	dopaminergic	x	x	0	0	x
metoclopramide	low	dopamin antagonist	dopaminergic	x	x	0	0	x
bupropion	high	norepinephrine and dopamine reuptake inhibitor	noradrenergic / dopaminergic	0	x	x	0	x
buspirone	high	serotonin 5-HT1A receptor partial agonist	serotonergic	x	0	0	0	x
clonidine	high	α2A-adrenergic receptor agonist	adrenergic	0	0	0	0	x
clonidine	low	α2A-adrenergic receptor agonist	adrenergic	0	0	0	0	x
yohimbine	high	α2-adrenergic receptor antagonist	adrenergic	0	x	0	0	x
sumatriptan	high	selective 5HT1 agonist	dopaminergic	x	0	0	0	x
tolcapone	high	COMT-inhibitor		x	x	x	x	x
doxepin	high	tricyclic antidepressive	serotonergic / noradrenergic	x	0	0	x	x

[1] high: the average of 15 mg and 30 mg doses; low: the average of 45 mg and 60 mg doses. [2]PD-AGO: pharmacodynamic agonism; PD-ANTA: pharmacodynamic antagonism; PK: pharmacokinetic interaction; RC: receptor cross-talk; AE: adverse effects. X: applicable; 0: not applicable.

4. Conclusion

In conclusion, this Delivery Report reveals the ten least effective combinations of augmentation drugs with morphine, emphasizing the significant impact of high morphine doses on efficacy and safety. Notably, metoclopramide and clonidine consistently ranked low across various morphine doses, indicating potential issues with both analgesic effects and adverse reactions. The analysis highlights key pharmacodynamic and pharmacokinetic interactions that may undermine the effectiveness of these combinations, including receptor competition and metabolic interference. Additionally, the findings underscore the importance of balancing therapeutic efficacy with the risk of adverse effects in drug pairings. Overall, while the model's predictions align with existing literature, further investigation is warranted to validate its accuracy in assessing synergistic effects.

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