QSPainRelief

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

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D2.1 'Report on CNS drug distribution and target engagement profiles of all candidate drugs for augmentation strategies'

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Abbreviations

BBB	blood-brain barrier
BCSFB	blood-CSF-barrier
BK	Binding kinetics
Cl	clearance of plasma compartment
CNS	central nervous system
Cp,ss	calculated total plasma concentration at steady state
Cp,u,ss	calculated unbound plasma concentration at steady state
Cb,u,ss	calculated unbound brain concentration at steady state
CM	cisterna magna
CSF	cerebrospinal fluid
ECF	brain extracellular fluid
F	fractional bioavailability
fAFBBB	multiplication factor between rate and human asymmetry factors
Foral	oral bioavailability
Fu	fraction unbound in plasma
ICF	brain intracellular fluid
IV	intravenous route of administration
ka	absorption rate constant, in cases of extravascular drug administration
KD	equilibrium dissociation constant between the drug and receptor
Kpuu	equilibrium (steady state) unbound concentration ratios between compartments
Kpuucm	ratio of unbound drug concentrations in plasma and CM at steady state
Kpuuecf	ratio of unbound drug concentrations in plasma and brain ECF at steady state
Kpuulv	ratio of unbound drug concentrations in plasma and LV at steady state
Kon	drug-receptor association rate constant
Koff	drug-receptor dissociation rate constant
LV	lateral ventricle
Mwt	molecular weight
PBPK	physiologically based PK
PBBK	physiologically based BK
PD	pharmacodynamic (drug effect -time profile)
PK	pharmacokinetics (drug concentration-time profile)
PO	*per os*, oral route of administration
SAS	subarachnoid space, including the lumbar CSF sampling region
τ	advised dosing interval
tmax	time at which the maximal concentration is reached
Vd	volume of distribution viewed from the plasma compartment

Table of Contents

Executive Summary

This report summarizes the assessment of the central nervous system (CNS) target site distribution (target site exposure) and target occupancies for part of the selected 107 candidate analgesic and augmentation drugs.

A critical component of the QSPainRelief project is to determine the concentration-time profile (PK) of each drug at each physiologically relevant target site compartment. CNS target site exposure is necessary to predict target engagement (i.e. occupancies), that will serve as an input for the neural circuit models of In Silico Biosciences, Inc. (ISB), to calibrate and predict the CNS effects of the drugs.

To predict CNS target site exposure in brain extracellular fluid (ECF), brain intracellular fluid (ICF), and cerebrospinal fluid (CSF) in the subarachnoid space (SAS), we use the physiologically based pharmacokinetic (PBPK) model, LEICNS-PK 3.0. The ***LEICNS-PK3.0*** model uses the drug properties and plasma PK for each individual drug. Plasma PK was calculated for various clinically relevant concentrations and dosing regimens. A full description of drug properties were obtained for 93 drugs to allow the LEICNS-PK3.0 model to generate single dosing target site predictions. Moreover CNS target site exposure predictions were made for 11 opioid drugs, including morphine, for multiple oral drug dosing regimens.

To predict target occupancies, the target site exposure of the drugs were used as input for physiologically-based target binding kinetic model ***LEICNS-PBBK1.0.*** This model uses target site exposure and receptor expression for 5 different CNS regions that are involved in the drug effects. The target occupancies in these 5 CNS regions could be predicted for 11 opioids. Due to the lack of receptor expression data on the other receptor types, alternative approaches are proposed for predictions of the target occupancies in the different CNS regions for the remaining drugs, and additional time is required to predict such target occupancies. Figure 1 provides a visualization of the CNS drug exposure and related target occupancy.

All data collected and predicted for CNS target site exposures and target occupancies are archived as extensive excel files and are made available for ISB neural circuit models while also stored in the QSPainRelief data base (WP3).

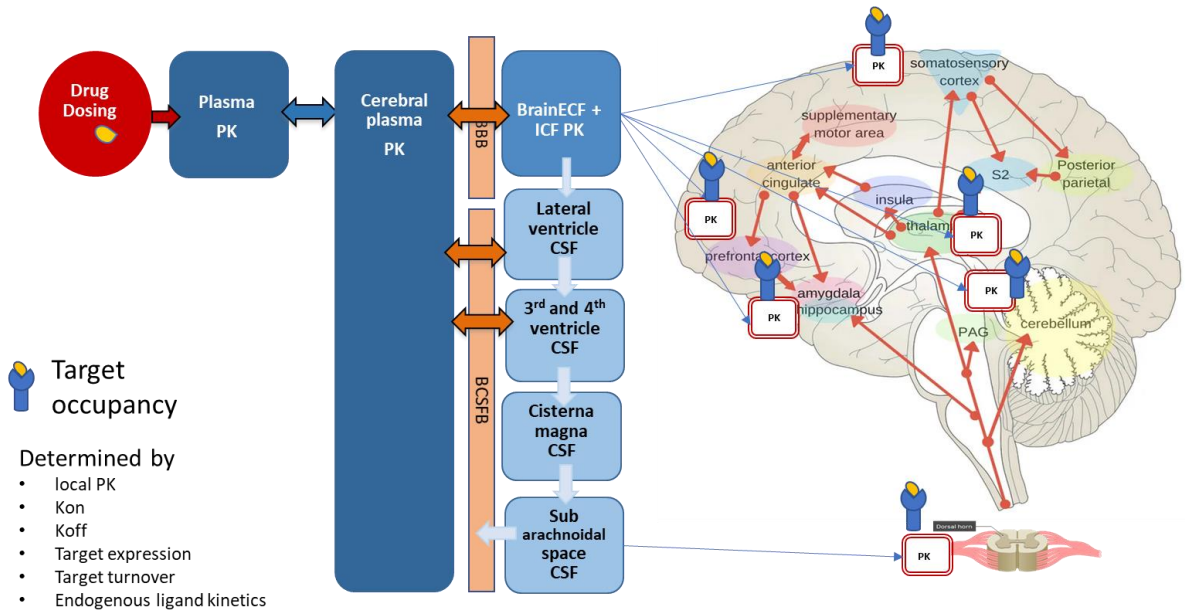

Figure 1-Schematic representation of CNS target site PK and resulting target occupancies.

Deliverable report

Determination of dosing and pharmacokinetic data for CNS target sites exposures

Using the physiologically based pharmacokinetic (PBPK) model, LEICNS-PK3.0, drug concentrations were predicted for ECF, ICF, and SAS. To this end, as input into the LEICNS-PK3.0 model (figure 2), the drug's *plasma PK* and the drug's properties were needed. To that end an extensive search was performed on literature and other publicly available data sources.

Plasma PK

Data on clinically relevant drug dosages were obtained from the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). Based on available data, an oral route of administration, i.e. PO, was selected as the preferred route of administration. For this, values for oral bioavailability (Foral) and the absorption rate constant (ka), as well as plasma PK models were needed. Plasma steady state concentrations were selected for drugs utilizing multiple daily administration periods. The plasma steady state concentration was calculated using the following equation:

$$Cp, ss = \left(\frac{Foral * D}{Cl * \tau}\right)$$

where D is the drug dose, Cl is the clearance rate of drug from the plasma compartment and τ is the advised dosing interval. Calculation of ka requires data on Cl, Vd (the volume of distribution viewed from the plasma compartment) and tmax (the time at which the maximal concentration is reached), and is based on solving the following equation for ka:

$$tmax = \frac{1}{ka - \left(\frac{Cl}{Vd}\right)}\left(ln\frac{ka}{\left(\frac{Cl}{Vd}\right)}\right).$$

Based on a thorough literature search it was found that out of the 107 medications on the QSPainRelief list of the selected analgesic and augmentation drug candidates, for 93 drugs the plasma PK could be predicted (Table 1). The other 14 drugs/metabolites did not possess sufficient data on PK properties to enable calculation of the necessary absorption rate constant (ka) required to predict bioavailability via extravascular drug administration. Also, pethidine was excluded based on redundancy as it was also listed as meperidine. Two morphine metabolites, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M3G) were excluded as these are morphine metabolites for which no adequate information was available (Table 2).

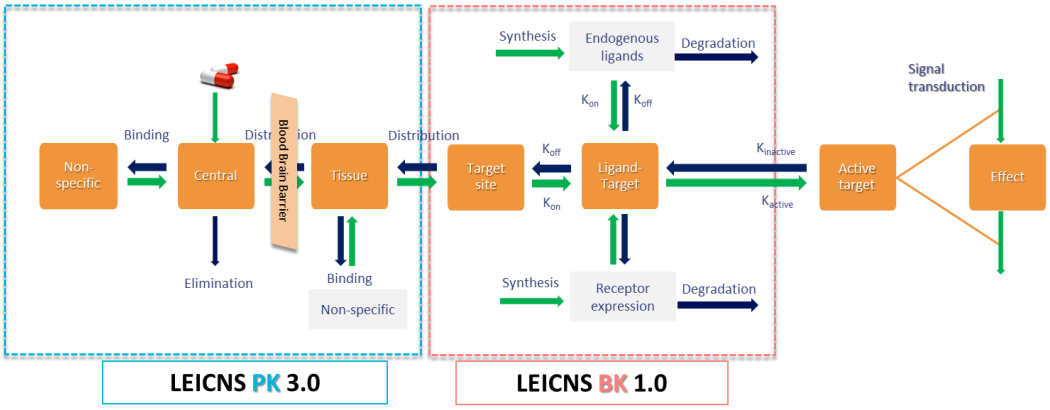

Figure 2. Schematic and simplified representation of the LEICNSPK3.0 and LEICONSBK1.0 mathematical models

Table 1. Overview of the 93 opioids and augmentation drugs for which plasma PK could be predicted, on the basis of the individual drug's oral bioavailability (Foral), absorption rate constant (ka), and plasma PK parameters.

nr	Drug	nr	Drug	nr	Drug	nr	Drug
1	alfentanil	26	brexpiprazole	51	ibuprofen	76	rivastigmine
2	buprenorphine	27	bumetanide	52	imipramine	77	rotigotine
3	codeine	28	bupropion	53	lacosamide	78	rufinamide
4	fentanyl	29	buspirone	54	levocetirizine	79	safinamide
5	hydrocodone	30	cannabidiol	55	lisuride	80	sertraline
6	hydromorphone	31	carbamazepine	56	maprotiline	81	esketamine
7	levorphanol	32	celecoxib	57	memantine	82	stiripentol
8	meperidine	33	citalopram	58	metoclopramide	83	sumatriptan
9	methadone	34	clomipramine	59	midazolam	84	tasimelteon
10	morphine	35	clonazepam	60	milnacipran	85	tolcapone
11	naltrexone	36	clonidine	61	mirtazapine	86	trazodone
12	oxycodone	37	desipramine	62	nalmefene	87	trimipramine
13	oxymorphone	38	desvenlafaxine	63	naproxen	88	varenicline
14	sufentanil	39	diazepam	64	nortriptyline	89	venlafaxine
15	tapentadol	40	diclofenac	65	paroxetine	90	vinpocetine
16	tramadol	41	donepezil	66	perampanel	91	vortioxetine
17	acetaminophen	42	doxepin	67	pindolol	92	yohimbine
18	agomelatine	43	duloxetine	68	pramipexole	93	zonisamide
19	alprazolam	44	escitalopram	69	pregabalin		
20	amantadine	45	fluoxetine	70	procyclidine		
21	amitriptyline	46	fluvoxamine	71	promethazine		
22	aripiprazole	47	gabapentin	72	rasagiline		
23	acetylsalicylic acid	48	galantamine	73	reboxetine		
24	atomoxetine	49	granisetron	74	retigabine		
25	baclofen	50	guanfacine	75	riluzole		

Table 2. Overview of the drugs that did not possess sufficient data on PK properties to enable calculation of the necessary absorption rate constant (ka) required to predict bioavailability via extravascular drug administration. Also, pethidine was excluded based on redundancy as it was also listed as meperidine. Two morphine metabolites, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M3G) were excluded as these are morphine metabolites for which no adequate information was available

nr	Drugs	CL	Vd	Tmax	ka	Foral	Fu	Comments
1	butorphanol			NA	NC			
2	amoxapine	NA	NA	NA	NC	NA		
3	dextromethorphan	NA	NA		NC		NA	No information on the active (R)-enantiomer
4	dihydroergocristine mesylate	NA	NA	NA	NC	NA		
5	pergolide	NA	NA		NC			
6	phenelzine	NA	NA		NC	NA		
7	piribedil	NA	NA		NC	NA	NA	
8	rimonabant	NA	NA	NA	NC	NA		
9	terguride						NA	
10	tranylcypromine						NA	
11	ziconotide			NA		NA		
12	M3G	NA	NA	NA	NA	NA	NA	metabolite
13	M6G	NA	NA	NA	NA	NA	NA	metabolite
14	pethidine							= meperidine
	NA = not available							
	NC = not computable							

Drug properties

For each of the 93 drugs for which plasma PK could be predicted, the following data on drug properties were collected from publicly available data sources: molecular weight, ion class, pKa, pKb, fraction unbound in plasma, Kpuu, ECF, Kpuu, LV, Kpuu, and CM, as needed to calculate the BBB/BCSFB transport asymmetry factors for each drug.

Kpuu values, defined as the ratio of unbound drug concentrations in a CNS compartment over the unbound drug concentrations in plasma at steady state (extent), for ECF, LV, and CM were collected from literature, and human values were collected if available, otherwise rat values that were translated to human values, and if no in vivo data was available, in vitro data were used, as in the workflow published by Yamamoto et al. (EJPS, 2018) and transporter expression ratios as published by Saleh et al (JPKPD, 2021). For three opioids, measured Kpuu values were available (morphine, codeine and oxycodone), while not for the other 8 opioids (alfentanil, buprenorphine, hydrocodone, hydromorphone, levorphanol, methadone, naltrexone and tapentadol). When no data on Kpuu values could be found or derived, the Kpuu values were assumed to be equal to 1 (thus only having passive BBB/BCSFB transport). Currently, approaches are being discussed on how to predict/generate Kpuu values based on drug physical chemical properties. We have selected the Brain Exposure Efficiency (BEE) approach. A software trial is requested, and we will evaluate the use of this approach for our purposes.

CNS target site exposure for ECF, ICF, and SAS

Using the physiologically based pharmacokinetic (PBPK) model, LEICNS-PK3.0, drug concentrations were predicted for ECF, ICF, and SAS. Table 3 provides the overview of the drugs included for single drug administration (milestone MS14) and multiple oral drug dosing more relevant to the standard of practice. Drug concentrations were provided in terms of the minimal (Cmin), the maximal (Cmax), and the average (Cav) concentrations for 11 opioids (Table 4), for day 14 and 15.

Table 3. Overview on drug dosing and CNS target site exposure predictions

		CNS target site exposure
Single drug dosing at relevant clinical doses	Type of dosing	Single dose, single administration
	(CNS) compartments	Plasma BrainECF BrainICF CSF-SAS
	Drugs	93 CNS active drugs (**MS14**)- see table 1
Steady state levels at relevant clinical doses	Type of dosing	Multiple dosing, based on clinical dosing regimen
	(CNS) compartments	Plasma BrainECF BrainICF CSF-SAS
	Drugs	11 opioids- see table 4
Multiple dosing at relevant clinical doses	Type of dosing	Multiple dosing, based on clinical dosing regimen
	(CNS) compartments	Plasma BrainECF BrainICF CSF-SAS
	Drugs	11 opioids- see table 4

** all dosing refers to oral dosing, except for alfentanil (IV administration for steady state and multiple dosing) and buprenorphine (including also buccal dosing for steady state and multiple dosing).*

Table 4. The 11 opioids or which single and multiple dosing administration was included in CNS target site exposures

11 Opioids	Alfentanil
	Buprenorphine
	Codeine
	Hydrocodone
	Hydromorphone
	Levorphanol
	Methadone
	Morphine
	Naltrexone
	Oxycodone
	Tapentadol

Determination of dosing and pharmacokinetic data for CNS target exposure

Using CNS target exposure to predict target occupancy by LEICNS-BK1.0 (figure 2) depends on binding kinetics data. The drug-receptor association and dissociation rate constants would be the best possible information because the association rate is concentration-dependent, and therefore important with changing concentrations at the target sites. Second best is the K_d (also denoted by KD) value which is the equilibrium dissociation constant between the drug and receptor (binding affinity). Extensive literature and database searches have shown that receptor expression data availability is scarce, especially for human and non-opioid receptors, and binding kinetic parameters for most of the drugs of interest are scarce too.

For the kinetic data situations described above, the drug target engagements could be predicted for 11 opioids at the mu-opioid receptor in 5 different regions of the CNS based on the drug (ligand) and receptor concentrations (table 5). Since not many drug Kon and Koff values have been reported, the receptor occupancy profiles were based on KD/Ki values. For uniformity, ISB has been and will be working with the same values for the drugs in the neural circuit models. The drug target effects were determined based on the following equations:

Bound receptor concentration, $$[LR] = \frac{([R_T] + [L_T] + K_D) - \sqrt{([R_T] + [L_T] + K_D)^2 - 4[R_T][L_T]}}{2}$$

where LR is the concentration of the receptor-ligand (drug) complex, RT is the total receptor concentration, LT is the total ligand (drug) concentration and KD is the equilibrium dissociation rate constant, and:

Receptor occupancy, $$RO = \frac{Bound\ receptor\ concentration}{Total\ receptor\ concentration} = \frac{[LR]}{R_T}$$

where RO is the receptor occupancy expressed as a fraction of the concentration of the receptor-ligand complex, LR, and the total receptor concentration RT.

Table 5. Overview on drug dosing and CNS target site exposure predictions and consecutive CNS target engagement (occupancy) predictions.

		CNS target site exposure	**CNS target engagement**
Single drug dosing at relevant clinical doses	Type of dosing	Single dose, single administration	Single dose, single administration
	CNS compartments/ regions	Plasma BrainECF BrainICF CSF-SAS	Cerebral cortex Thalamus Midbrain Pons & Medulla Spinal cord
	Drugs	93 CNS active drugs (**MS14**)	11 opioids
Steady state levels at relevant clinical doses	Type of dosing	Multiple dosing, based on clinical dosing regimen	Multiple dosing, based on clinical dosing regimen
	CNS compartments/ regions	Plasma BrainECF BrainICF CSF-SAS	Cerebral cortex Thalamus Midbrain Pons & Medulla Spinal cord
	Drugs	11 opioids	11 opioids
Multiple dosing at relevant clinical doses	Type of dosing	Multiple dosing, based on clinical dosing regimen	Multiple dosing, based on clinical dosing regimen
	CNS compartments/ regions	Plasma BrainECF BrainICF CSF-SAS	Cerebral cortex Thalamus Midbrain Pons & Medulla Spinal cord
	Drugs	11 opioids	11 opioids

** all dosing refers to oral dosing, except for alfentanil (IV administration for steady state and multiple dosing) and buprenorphine (including also buccal dosing for steady state and multiple dosing).*

An overview of the predicted plasma PK, CNS target sites PK, and CNS target occupancies is provided in the supplementary table at the end of this report.

For the rest of the 93 drugs, receptor occupancies could not be predicted due to lack of adequate data on receptor expressions. As a mitigation plan, a hierarchy plan was made (figure 3), where, for example, in cases where receptor protein expression data are not available, mRNA expression was to be used for the predictions.

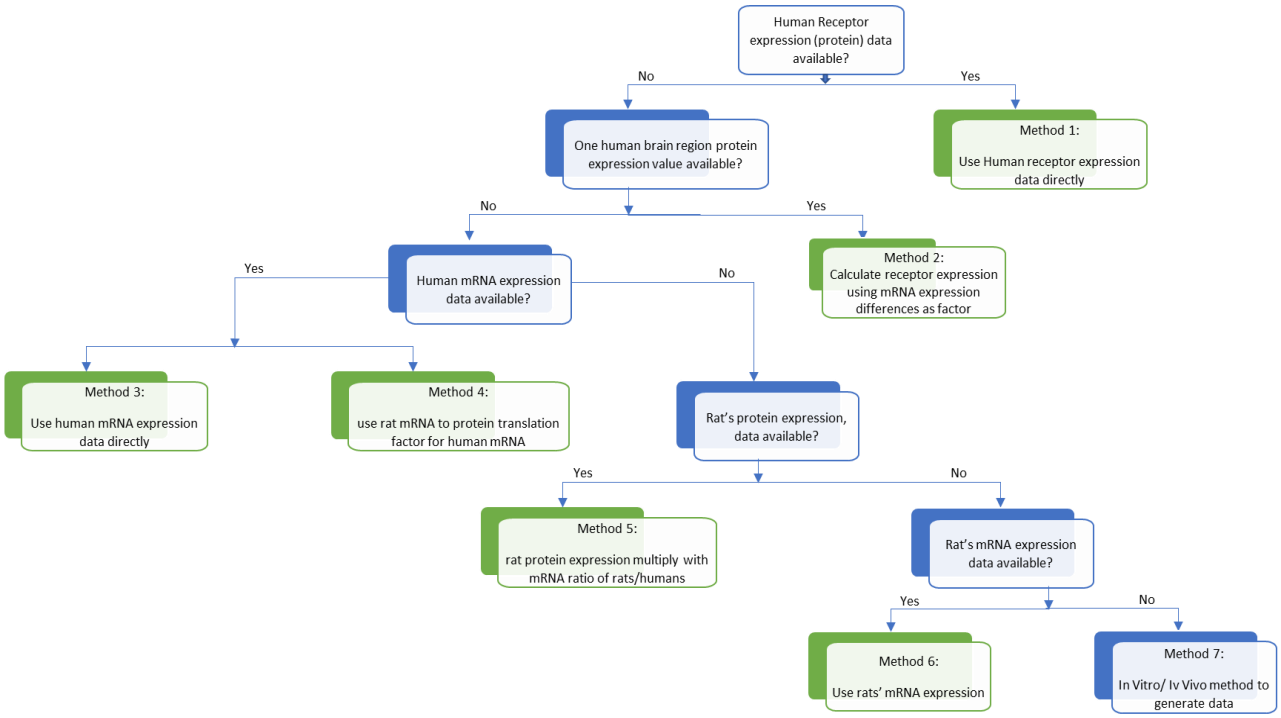

Figure 3. Workflow on what to use as (biomarker of) receptor expression.

However, also identifying mRNA expression of mu-opioid receptors in absolute quantitative terms was a time-consuming task, due to lack of useful data from literature/databases.

Conclusion

Extensive data collection efforts have been put into searching for the right data to ultimately provide CNS target site exposure and engagement of as many individual candidate analgesic and augmentation drugs as selected for the QSPainRelief project.

The LEICNS-PK 3.0 model was successful in providing critical data on the PK profiles of 93 drugs in plasma, brainECF, brainICF and SAS, following single dose oral administration. In addition, multiple dose administration was used for 11 opioids for plasma, brainECF, brainICF and SAS PK profiles. For the drugs where no information was available nor could be derived for Kpuu values, it was so far assumed that the Kpuu values would be 1 (indicating passive transport across BBB and BSCFB only). Additional effort will be put into using in silico approaches to have estimates of these Kpuu values.

The PK information for these 11 opioids is used to predict their target occupancies in multiple relevant regions of the brain and spinal cord where the binding kinetic data were available as well as the receptor expression data. For the remaining drugs, such information is missing, and alternative approaches are being worked on and explored.

Supplemental material

S1: ***List of opioids and dose regimens for which target site concentrations were modeled by LeiCNS-PK3.0 and target engagement in different brain regions were modeled by LeiCNS-BK1.0 model.***

Drug	dose	dose units	dosing frequency	Route of administration	CNS target site PK			Mu opioid receptor occupancy profile				
					BrainECF	BrainICF	CSF in SAS	Cerebral cortex	Thalamus	Midbrain	Pons & Medulla	Spinal cord
alfentanil	0,5	mg/kg/day	prn	iv	yes	yes	yes	yes	yes	yes	yes	yes
	5	ug/kg/day	prn	iv	yes	yes	yes	yes	yes	yes	yes	yes
	10	ug/kg/day	prn	iv	yes	yes	yes	yes	yes	yes	yes	yes
	100	ng/ml/day	qd	iv	yes	yes	yes	yes	yes	yes	yes	yes
buprenorphine	2	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	2	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	2	mg/day	tid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	4	mg/day	qid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	16	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	60	ug/day	bid	buccal	yes	yes	yes	yes	yes	yes	yes	yes
	75	ug/day	bid	buccal	yes	yes	yes	yes	yes	yes	yes	yes
	120	ug/day	bid	buccal	yes	yes	yes	yes	yes	yes	yes	yes
	150	ug/day	bid	buccal	yes	yes	yes	yes	yes	yes	yes	yes
	180	ug/day	bid	buccal	yes	yes	yes	yes	yes	yes	yes	yes
	240	ug/day	bid	buccal	yes	yes	yes	yes	yes	yes	yes	yes
	300	ug/day	bid	buccal	yes	yes	yes	yes	yes	yes	yes	yes
	450	ug/day	bid	buccal	yes	yes	yes	yes	yes	yes	yes	yes
	600	ug/day	bid	buccal	yes	yes	yes	yes	yes	yes	yes	yes
	750	ug/day	bid	buccal	yes	yes	yes	yes	yes	yes	yes	yes
	900	ug/day	bid	buccal	yes	yes	yes	yes	yes	yes	yes	yes
codeine	8	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	15	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	30	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	60	md/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	200	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	300	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	400	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
hydrocodone	2,5	mg/day	tid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	5	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	10	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	15	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	20	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	20	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	30	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	40	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	45	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	50	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	60	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	90	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	120	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
hydromorphone	2	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	4	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	6	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	8	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	12	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	16	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	18	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	24	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	32	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	40	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	48	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	64	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes

levorphanol	1,2	mg/day	tid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	3,15	mg/day	tid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	3,5	mg/day	tid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	13,5	mg/day	tid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	15,75	mg/day	tid	oral	yes	yes	yes	yes	yes	yes	yes	yes
methadone	5	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	10	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	20	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	30	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	40	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	50	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	50	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	60	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	70	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	80	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
morphine	10	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	15	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	30	mg/day	qpm	oral	yes	yes	yes	yes	yes	yes	yes	yes
	30	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	30	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	45	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	60	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	90	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	120	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
naltrexone	2,4	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	3,4	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	4,5	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	19,2	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	40	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	50	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	100	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	150	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
oxycodone	10	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	10	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	20	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	20	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	30	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	30	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	40	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	40	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	50	mg/day	qd	oral	yes	yes	yes	yes	yes	yes	yes	yes
	80	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	120	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
tapentadol	200	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	400	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes
	500	mg/day	bid	oral	yes	yes	yes	yes	yes	yes	yes	yes

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