QSPainRelief

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

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Abbreviations

ADME	absorbed, distributed, metabolized, excreted
AI	artificial intelligence
BBB	blood-brain barrier
BCRPs	breast cancer resistance proteins
BCSFB	blood-CSF barrier
BK	binding kinetics
BOLD	blood-oxygen-level dependent (imaging technique)
brainECF	brain extracellular fluid
brain ICF	brain intracellular fluid
brainMV	brain microvascular space
CBF	cerebral blood flow
CSF	cerebrospinal fluid
concentris	concentris research management gmbh
CNS	central nervous system
CUI	clinical utility index
EEG	electroencephalography
GPCRs	G-protein-coupled receptors
ICD	International Classification of Diseases
IIB	Impact and Innovation Board
ISB	In Silico Biosciences, Inc.
MOR	mu-opioid receptor
MW	molecular (mass) weight
MRI	magnetic resonance imaging
MRPs	multidrug resistance proteins
NSAID	non-steroidal anti-inflammatory drugs

multidrug resistance proteins (MRPs), and breast cancer resistance proteins (BCRPs

PET	Positron Emission Tomography
P-gp	P-glycoprotein
PK-PD	Pharmacokinetics-Pharmacodynamics
QSP	Quantitative Systems Pharmacology
SAS	subarachnoid space
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ULEI	Universiteit Leiden
WP	Work package

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1. Executive Summary

Chronic pain affects nearly one in five Europeans and remains a major clinical and societal challenge due to its complex pathophysiology and the limited efficacy of current treatments. Opioids, while widely used, present significant risks and often fail to provide lasting relief. Combination therapies offer a more rational approach, targeting multiple mechanisms to improve outcomes and reduce side effects. However, identifying effective drug combinations is hindered by biological variability, limited clinical trial data, and poor translation from animal models.

QSPainRelief proposes an innovative, model-based solution using Quantitative Systems Pharmacology (QSP) to simulate and predict the effects of CNS-active drug combinations in silico. By integrating pharmacokinetic, pharmacodynamic, and neural circuit models, including patient-specific factors, QSPainRelief aims to optimize combination strategies and support personalized pain management. While promising, the approach still faces challenges, particularly the need for better biological understanding of chronic pain mechanisms and their incorporation into QSP models. Nonetheless, this initiative marks an important step toward more effective, safer, and individualized therapies for chronic pain.

2. Deliverable Report

2.1. Introduction

2.1.1. Chronic pain and its impact on patients and healthcare

Chronic pain, defined as pain lasting longer than three months, is one of the most prevalent and complex medical conditions[1]. It affects about 20% of the European population, particularly women and older adults[2, 3]. Chronic pain severely impacts quality of life, limits mobility, disrupts daily activities and social interactions, and is associated with mental health comorbidities such as depression[4, 5].

The socio-economic burden of chronic pain is major, costing up to €300 billion annually in Europe due to increased healthcare use, productivity loss, and premature workforce exit[6, 7]. This underscores the urgent need for more effective and sustainable treatment strategies.

An important step towards improved recognition and diagnosis of chronic pain has been its inclusion in the 11th edition of the International Classification of Diseases (ICD-11). This new classification formally distinguishes between chronic primary pain (a disease in its own right) and chronic secondary pain (in which pain is a symptom secondary to an explained medical condition such as chronic pain following surgery or injury)[8].

Chronic pain is a multifactorial condition encompassing biological, psychological and social factors which must be apprehended using a biopsychosocial framework. The pathophysiology of chronic pain involves a complex combination of genetic, physiological, neurochemical, and inflammatory mechanisms[9, 10]. Central and peripheral sensitization, along with psychological factors such as anxiety or pain catastrophizing, contribute to chronicity and poor treatment outcomes[11-14]. This intricate interplay of biological and psychological dimensions contributes to the challenge of effectively managing chronic pain and highlights the limitations of current therapeutic strategies[15].

2.1.2. Limited efficacy of current treatments

The primary goals in chronic pain management are to reduce pain, improve function, and enhance overall quality of life while minimizing treatment-related side effects. Treatment strategies include both pharmacological (e.g., opioids, antidepressants, anticonvulsants, NSAIDs) and non-pharmacological approaches[16-18].

Despite the available treatment options, about 60% of patients report insufficient relief, and many discontinue treatment due to adverse effects[2].

The limited efficacy of current treatments is thought to be related to the complexity and heterogeneity of chronic pain conditions. Patient-specific factors such as age, sex, genetic background but also psychosocial factors, significantly influence both susceptibility and treatment response and many trials fail to demonstrate consistent efficacy across populations[19-21].

As a result, there is increasing interest in mechanism-based approaches and better patient stratification[22].

2.1.3. Opioid-based treatments for chronic pain

Opioids, despite their proven efficacy in treating nociceptive and mixed pain conditions, such as cancer-related pain, present numerous clinical challenges[23]. Long-term opioid therapy is associated with significant risks, including the development of tolerance (requiring escalating doses for the same effect), physical dependence, and the potential for addiction. Moreover, opioid-induced side effects such as constipation, sedation, respiratory depression, and cognitive impairment can severely impact patients' quality of life and limit treatment adherence.[12] These complications are especially concerning in chronic pain populations, where extended treatment durations increase the likelihood of adverse outcomes[12]. A substantial proportion of patients treated with oral morphine report insufficient analgesia, intolerable side effects, or both, underscoring the need for alternative strategies in chronic pain management[24].

Moreover, many patients report insufficient analgesia or intolerable adverse effects with opioids such as oral morphine, underlining the need for better alternatives. Long-term opioid use is strongly linked to dependence, and addressing this issue has become a public health priority. Agencies such as the CDC and FDA advocate for safer and more effective treatment regimens**.**

2.1.4. Combination therapies

Most analgesics cannot be prescribed at unlimited doses due to ceiling effects and safety concerns. Furthermore, single-drug treatments cannot adequately address the multiple pathways involved in pain pathogenesis[25]. Many agents also impair mobility, memory, and physical activity, all of which are essential for rehabilitation[26].

The development of new analgesics remains slow and uncertain. Drug discovery in this field is challenging and has not yielded a new class of approved agents in decades. The approval rate for CNS-active drugs is about 14%, lower than the general average of 20%[27].

Given these limitations, combination pharmacotherapy has emerged as a promising strategy. Formally described in the 1980s and popularized by Kehlet and Dahl, combination pharmacotherapy or "multimodal analgesia" is recommended for with partial or inadequate responses to monotherapy[28]. The rationale for this recommendation is that targeting multiple pain mechanisms may enhance efficacy, and combining drugs at lower doses may improve safety and tolerability. Evidence indicates that more than 50% of chronic pain patients receive at least two medications concurrently.

Mechanistically, chronic pain involves both excitatory and inhibitory pathways[29]. Treatments like opioids enhance inhibition, while drugs like gabapentin or pregabalin reduce excitation[30, 31]. A rational combination approach might involve targeting both peripheral and central mechanisms to block pain transmission and modulate its effects centrally. Frequently used combinations include paracetamol with opioids, NSAIDs with opioids, muscle relaxants with opioids, and various antidepressant-anticonvulsant pairings[32, 33].

However, rigorous clinical trials assessing these combinations remain scarce, and there is an urgent need for systematic, mechanism-based approaches to identify, assess, and personalize

combination therapies – ultimately aiming for more effective and tailored chronic pain management. Available evidence for the effectiveness of treatment combinations is variable. While some pairings outperform their individual components, others do not, underlining the importance of combination-specific research[34]. Systematic reviews and meta-analyses on this topic often reach inconclusive results, hindered by small sample sizes, data heterogeneity, and lack of placebo-controlled designs. Moreover, many trials fail to compare both components individually, limiting our ability to draw robust conclusions[32].

Studies comparing opioid monotherapy with opioid-non-opioid combination therapy have provided insights into optimizing pain management strategies. Some reviews suggest that combining opioids with non-opioid analgesics, such as NSAIDs or acetaminophen, can enhance analgesic efficacy while reducing the required opioid dose, thereby mitigating associated risks such as tolerance, dependence, and adverse effects[35-37].

2.1.5. Quantitative Systems Pharmacology (QSP): A model-driven approach to optimise combination treatments

The sheer number of possible drug-dose combinations presents a major challenge. For example, testing just three doses of an opioid with three doses of one of 20 augmentation drugs would already require 180 combinations. Including multiple opioids, more augmentation agents, and accounting for patient characteristics such as age, sex, or pain aetiology increases this number exponentially. Exhaustive exploration through animal studies or clinical trials is therefore impractical due to cost, time, and feasibility constraints.

While big data might appear as an alternative, real-world data remain sparse for many combinations and rarely provide mechanistic insights. To address this, we propose a model-driven approach based on Quantitative Systems Pharmacology (QSP).

QSP is an interdisciplinary and holistic modelling approach that studies drug effects on the complex interactions within and between biological systems, from the molecular to the population level, using advanced mathematical and computational tools. It represents a powerful convergence of pharmacology and systems biology, aiming to understand and predict therapeutic and adverse effects in a mechanistic and integrative manner.

QSP integrates multiple layers of biological knowledge, encompassing pharmacokinetics/pharmacodynamics (PK/PD), physiologically based pharmacokinetics

(PBPK) models, and biophysically realistic neural models, to simulate drug action across biological scales. These models can link drug dosing to time-dependent brain concentrations, target engagement, and downstream physiological and behavioural effects.

PBPK models predict how drugs are absorbed, distributed, metabolized, and excreted (ADME), as well as their kinetics at target sites within the central nervous system (CNS). These outputs – such as receptor occupancy over time – are then fed into spiking neuronal network models to simulate system-level outcomes including analgesia, sedation, cognitive impairment, and abuse liability.

QSP relies on dynamic, mechanistically grounded modelling to build realistic, knowledge-based simulation platforms. These platforms are increasingly used across biomedical sciences to support drug discovery, understand disease mechanisms, and anticipate patient-specific treatment responses, including those influenced by age, sex, genetics, or comorbidities.

By leveraging these multi-scale models, researchers can simulate and predict clinical outcomes *in silico*, significantly accelerating and focusing experimental efforts. This stepwise modelling, from drug dosing to target exposure, neural response, and clinical prediction, is illustrated in **Figure 1**.

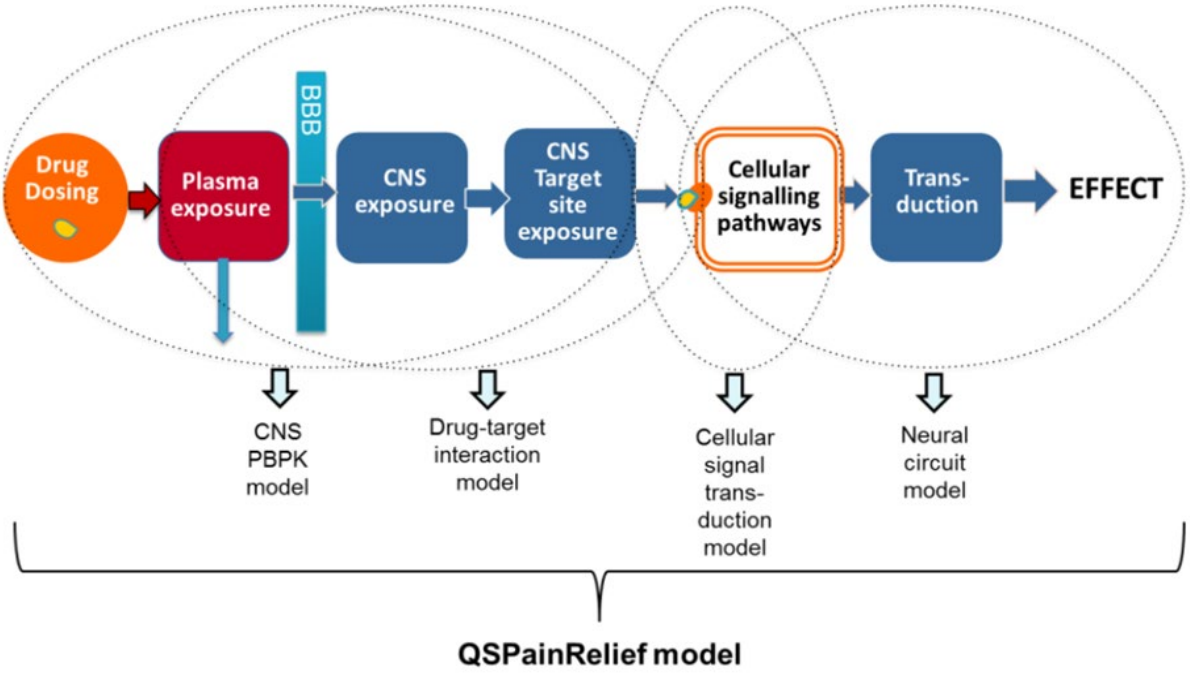


***Figure 1**. QSP modelling from drug dosing to systems effect.*

2.2. The QSPainRelief project

QSPainRelief is an H2020-funded research project aiming at developing a QSP approach for the development of optimal combination treatments for chronic pain[38-40]. The QSPainRelief platform is an in-silico simulation platform capable of predicting in individual patients the effects of novel CNS-active drug combinations, with a specific focus on opioid-non-opioid combinations[41, 42].

QSPainRelief brings together expertise from academia, industry, clinical practice, and patient organizations to construct multiscale models that reflect drug actions from target site engagement to system-level responses. The platform aims to advance scientific understanding, reduce reliance on costly and slow trial-and-error methods in clinical development, guide clinicians, and inform healthcare and regulatory decisions.

By integrating patient-specific factors such as age, sex, and psychosocial traits, the platform supports a personalized medicine approach, tailoring treatment combinations to maximize efficacy while reducing adverse effects.

Ultimately, QSPainRelief aims for a shift towards more mechanistically-informed and patient-centred pain management strategies. In analgesic drug development, empirical correlations between drug exposure and clinical pain scores are usually characterized by PK-PD models for clinical pain. The latter estimate parameters such as the maximal analgesic effect, the concentration of half-maximum effect, and the effect-site equilibration rate constant, which help to quantitatively explain analgesic exposure-response relationships. To facilitate personalized treatment, these models may additionally incorporate predictors of the inter-individual variability of these parameters (e.g.: age, body weight, or organ function). However, most PK-PD models do not explore the causal relationship or the mechanistic basis between the various elements influencing pain perception. Consequently, their application for translational purposes – that is, making predictions across species or patient populations – is limited. Nevertheless, in certain PK-PD studies, biomarkers are employed as a mechanistic link between drug exposure and clinical response; thus, they have important advantages in terms of translation and prediction. However, as pain is a problem with various interacting components, only PK-PD models are not enough. The complete characterization of pain and its pharmacological, physiological, and psychological processes is made possible by using QSP approaches[41].

QSP models have improved properties for translation and prediction since they can enable the simultaneous analysis of multiple clinical studies in comparable pain conditions. Findings and biomarkers that may be applied to various patient populations would be especially helpful for those who are unable to self-report their pain.

In drug development, QSP models might help to identify and validate new drug targets or suggest suitable combinations of existing drugs. Furthermore, they would provide a better basis for the prediction of optimal dose regimens and translation (e.g., preclinical to clinical or between different human populations). Lastly, the translational performance of preclinical pain models may be enhanced by the biomarkers derived from QSP methods[41].

Computational pharmacology thus has the potential to address some of the challenges of analgesic drug discovery. It can elucidate pain mechanisms, guide the analgesic target selection, analyse the chemical structural data about ligands and proteins to design more effective and safer analgesics, predict the analgesics' mechanism of action and adverse effects, facilitate the animal-to-human translation, and patient stratification[27].

2.3. The QSPainRelief modelling platform

2.3.1. Integrating pharmacokinetics and systems pharmacology

2.3.1.1. Overview of PBPK and QSP models

PBPK models represent the organism as interconnected compartments (e.g., liver, kidney, brain) and simulate absorption, distribution metabolism and excretion (ADME) processes using physiological flows and anatomical features[43]. By incorporating detailed individual biological parameters, they can account for inter-individual variability, including species, age,

sex, genetics, and disease states[44]. This mechanistic foundation makes PBPK models highly relevant for translating animal or in vitro data to humans[45].

Typical PBPK inputs include

- Drug-specific parameters: molecular mass weight (MW), ionization constants pKa/pKb, lipophilicity (LogP), polar surface area, H-bond donors/acceptors.
- System-specific parameters: organ volume, blood flow, membrane properties, pH.
- Biological parameters: plasma protein binding, tissue binding, receptor affinities, transporter activity.
- Kinetic parameters: absorption rates, elimination constants, and enzyme kinetics such as Michaelis–Menten parameters.

Together, these parameters determine drug kinetics at the compartmental level and are thus essential to predict CNS exposure [46].

While PBPK provides detailed pharmacokinetics, it often misses system-level effects like cellular feedback or disease dynamics. QSP, on the other hand, models drug effects on biological systems at a broader level. It simulates how drugs influence complex networks, such as receptor binding, signalling pathways or gene expression. It combines data from molecular biology, pharmacology, and clinical research. By integrating PBPK's in-depth pharmacokinetics with QSP's systems-level understanding, the combined approach offers a comprehensive framework for understanding drug action across diverse scenarios.

2.3.1.2. CNS drug distribution and implementation in QSPainRelief

Multiple factors govern the transport of drug molecules into and out of the CNS, and their distribution within it. Physiological CNS compartments include the brain microvascular space (brainMV), brain extracellular fluid (brainECF), brain intracellular fluid (brainICF), and several cerebrospinal fluid (CSF) spaces. CNS drug distribution depends on physiological fluid flows, passive and active transport across the blood-brain barrier (BBB) and blood-CSF barrier (BCSFB), extracellular–intracellular exchange, and pH gradients. Physiological fluid flows include cerebral blood flow (CBF), brainECF bulk flow, and CSF flow[47].

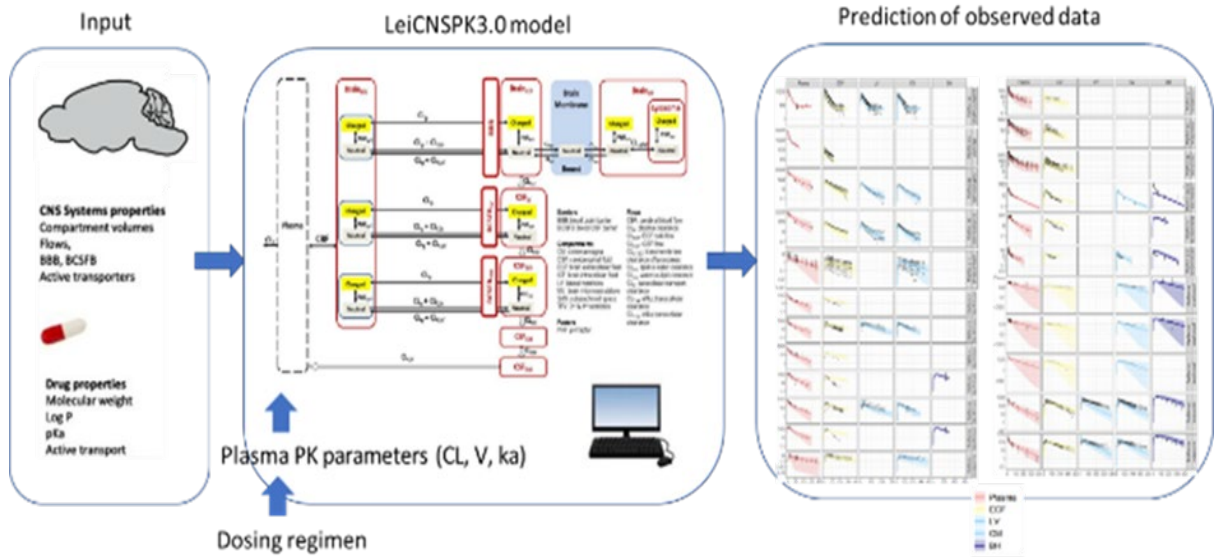
For the QSPainRelief platform, we integrate the CNS PBPK model (LeiCNS-PK3.0) with QSP neural circuit models covering analgesia, sedation, cognition, and abuse liability. These models require target occupancy data, which depends on target-site exposure, expression, and binding kinetics[48].

The LeiCNS-PK3.0 model is currently the most comprehensive CNS PBPK model available. It includes compartments for the brain microvasculature, BBB, BCSFB, brainECF, brain cells, subcellular lysosomes, and CSF in lateral ventricles, third and fourth ventricles, cisterna magna, and subarachnoid space[49, 50].

This model captures both bound/unbound and ionized/unionized drug species in each compartment, enabling accurate predictions of CNS drug kinetics. It supports the estimation

of CNS target-site exposure based on plasma PK profiles and brain barrier properties. Combined with data on target expression and binding kinetics (association/dissociation rates), the model enables prediction of target occupancy, a critical input for QSP-based simulation of pharmacodynamic outcomes[48]. The LeiCNS PBPK 3.0 model predictions are shown for examples for rat (**Figure 2A**) as well as human (**Figure 2B**), with predictions being within 2-fold error of actually observed data in humans from other studies.

A.



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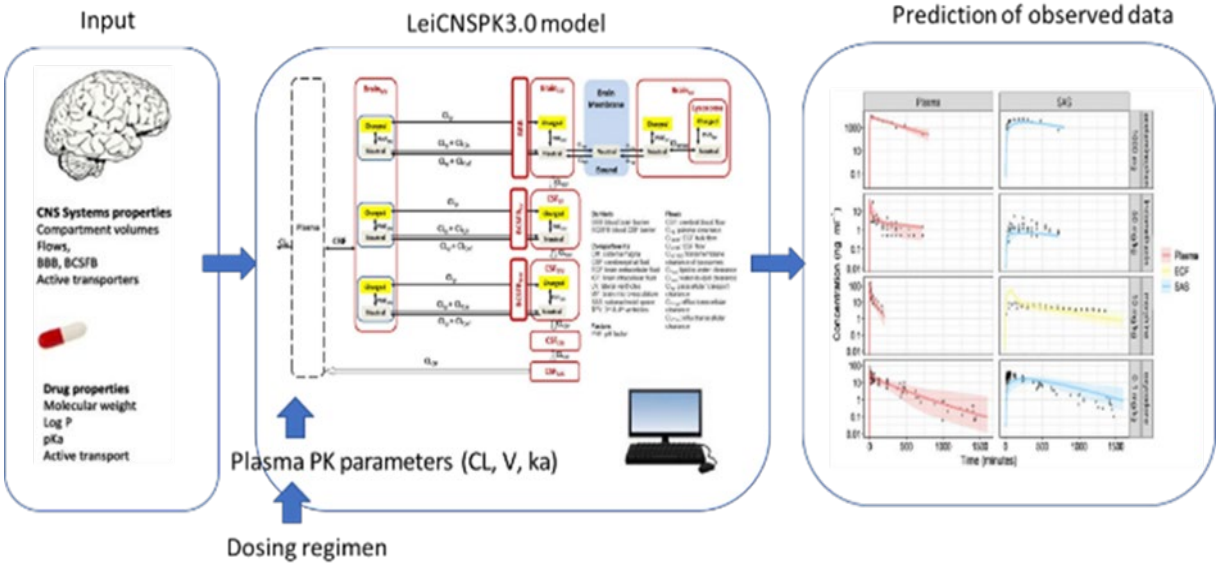

***Figure 2**. The LeiCNSPK3.0 physiologically based pharmacokinetic model uses CNS system-specific properties, drug-specific properties, and plasma PK parameters to predict CNS-region specific predictions of drug disposition and has been validated for both (**A**) rat and (**B**) humans.*

With a given plasma PK profile for a certain dose regimen, and information on the extent of drug distribution at the brain barriers, this model can be used to predict CNS target site exposure (PK profiles) at relevant target sites. Combined with target expression for a certain CNS region, and drug specific target association and dissociation rate constants, the target occupancy profiles can be predicted.

2.3.2. CNS drug distribution: from plasma to target site

2.3.2.1. Plasma pharmacokinetics and brain entry

The concentration-time profile (PK) of unbound drug concentrations in plasma plays a crucial role in drug transport across brain barriers. The neutral unbound drug molecules can pass the cell membranes of the brain barriers, while all unbound molecules (if small enough) can pass between the barrier cells.

2.3.2.2. Transport across the blood brain barrier

The BBB and BCSFB regulate the movement of drugs into and out of the brain. While structurally distinct, formed by endothelial cells (BBB) and choroid plexus epithelial cells (BCSFB), both regulate transport based on molecular properties such as lipophilicity, size, shape, charge, and transporter affinity.

Drug transport mechanisms include:

- Simple diffusion, a passive process that moves drug molecules along a concentration gradient, from areas of high to low concentration. Only unbound and sufficiently small or lipophilic molecules can cross membranes this way. For hydrophilic drugs, movement is strongly restricted by tight junctions, limiting paracellular transport across the BBB.
- Facilitated diffusion, also a passive process, which requires specific transporter proteins to carry molecules across membranes. This process is saturable: once all transporter sites are occupied, additional substrate cannot increase the rate. Facilitated diffusion plays a role in transporting substances like amino acids, monocarboxylates, nucleosides, and small peptides across the BBB.
- Fluid Phase (vesicular) Transport Fluid encompasses processes like pinocytosis, adsorptive-mediated endocytosis, and receptor-mediated endocytosis. While generally minimal in the BBB, receptor-mediated transport allows specific large molecules to cross via vesicles. These vesicles may either deliver their content into the brain or be degraded before release.
- Active Transport, an energy-dependent mechanism that moves drugs against their concentration gradient via membrane-bound transport proteins, involves membrane transport proteins that specifically bind and transport molecules against concentration gradients. This process is temperature-sensitive and can become saturated. Active transport can be influenced by competitive and non-competitive inhibitors and protein phosphorylation. Transport proteins are critical in drug development and play a

significant role in maintaining brain homeostasis for endogenous compounds. However, many drugs are also ligands for these transporters.

- Efflux transporters, such as P-glycoprotein (P-gp), multidrug resistance proteins (MRPs), and breast cancer resistance proteins (BCRPs), have garnered attention due to their impact on drug distribution across the BBB. These transporters limit brain distribution of many drugs, even those that are lipophilic and should, in theory, diffuse passively.

2.3.2.3. Cerebral Blood Flow and Effective Capillary Surface Area

For drugs with high BBB permeability, cerebral blood flow becomes the rate-limiting factor for brain entry. Blood flow can be influenced by the linear flow rate or the number of perfused capillaries. Increased blood flow velocity enhances the influx of highly permeable drugs across the BBB, while the transport of less permeable drugs remains largely unchanged. Variations in capillary perfusion ("effective perfusion") can affect BBB transport for all drugs.

2.3.2.4. Intra-CNS Distribution and Brain Tissue Binding

Intra-CNS distribution refers to all processes occurring after a drug crosses the brain barriers. It involves several mechanisms:

- CSF Turnover and ECF Bulk Flow. Cerebrospinal fluid (CSF) is produced by the choroid plexus and reabsorbed into the bloodstream through the arachnoid villi. CSF turnover can lower drug concentrations in the CSF. The slower the drug permeation into the CSF, the greater the impact of CSF turnover on CSF drug levels relative to plasma concentrations. Since CSF turnover is slower than trans-capillary transport, extracellular fluid (ECF) concentrations in the brain equilibrate more quickly with plasma concentrations than with CSF. Moreover, ECF bulk flow into the CSF can counteract molecular diffusion from CSF back into brain tissue.
- Extra-Intracellular Exchange and Brain Tissue Binding. Drugs may preferentially distribute between extracellular and intracellular spaces and may bind non-specifically to brain tissue components. Drug distribution between these compartments occurs through both simple diffusion and active transport. The distribution of drugs is important for determining the concentration of unbound drug at the target site, which is crucial for optimizing therapeutic effects.
- Drug Metabolism. Metabolic activity within the CNS also affects intra-CNS distribution. Enzymes in the BBB, BCSFB, and ependymal cells may act as barriers, metabolizing drugs before they enter the brain. Additionally, the brain vasculature contains cytochrome P450s, monooxygenases, and conjugating enzymes such as UDP-glucuronosyltransferase and glutathione S-transferase. The choroid plexus is particularly active metabolically; its enzymatic profile resembles that of the liver and can significantly influence CNS drug disposition.

2.3.3. Drug target engagement

Binding kinetic (BK) models are used to determine how and where drugs engage their targets in the brain. In the QSPainRelief project, as an initial focus, we modelled opioid binding to mu-opioid receptors (MOR), using drug concentrations in the extracellular fluid (ECF) and subarachnoid space (SAS) derived from PBPK outputs[51]. Combining these with receptor affinities and MOR expression levels across brain regions, we calculated the regional fraction of occupied receptors.

For dopaminergic, serotonergic, noradrenergic and muscarinic receptors, a mathematical generic synapse model was used[52]. It was calibrated through fast-cyclic voltammetry (preclinical data) and constrained by human PET imaging data obtained using selective postsynaptic probes. Drug effects were modelled as competition with endogenous neurotransmitters (e.g., dopamine, serotonin), based on brain drug concentrations and receptor affinities.

To guide the development of combination therapies for chronic pain, a deeper understanding of the molecular mechanisms underlying drug synergy is essential. In particular, receptor heteromerization – the ability of two G protein-coupled receptors (GPCRs) to form functional heterodimers – has been proposed as a key biological mechanism that could explain drug cooperativity in pain pathways[53-55].

In this context, the QSPainRelief project explored heteromerization as a mechanistic basis for drug interaction. Two complementary strategies were employed:

- A mathematical modelling approach, where formal frameworks for binding and functional cooperativity between ligands acting on heterodimeric receptors were developed, under both equilibrium and non-equilibrium conditions[56, 57].

- A structural modelling approach, using coarse-grained molecular dynamics simulations to investigate the self-assembly of mu-, delta-, and kappa-opioid receptors with the cannabinoid CB1 receptor (submitted manuscript).

These approaches help capture drug interactions at the molecular level, integrating receptor dynamics into larger pharmacological and systems models. Their inclusion within the QSP platforms strengthens the capacity to predict when and how drug combinations will exhibit synergy or antagonism. Ultimately, combining such mechanistic insights with in vitro and in vivo data offers a path toward more precise, safer, and effective multimodal analgesic strategies.

2.3.4. Integration into QSP neural circuit models

Once drug–receptor interactions are established, their effects can be integrated into biophysical neural network models that simulate neuronal activity as shown in Figure 3 [58]. Drug-induced receptor activation changes lead to ion-channel conductance variations via a transfer function:

$$\mathbf{gn} = \mathbf{g} * \mathbf{ParamYZ} * (1 +/- \mathbf{NYA})$$

where **gn** is the new conductance for channel Z, **g** is the baseline conductance, **NYA** is the normalized change in activation of receptor **Y**, using addition or subtraction depending on whether **Y** increases or decreases the conductance of channel **Z**. NYA is based on control activation level XYC and activation with drug XYA so that **NYA** = (XYA - XYC)/XYC. **ParamYZ** optimizes the correlation of platform output with clinical outcomes. The platform output captures variation of clinical experiments related to neurological outcomes/activity (**Figure 3**).

The platform is based on Hodgkin-Huxley-type neuron models, modulated by neurotransmitter systems with accurate anatomical and receptor localization. It currently includes over 30 molecular targets across key CNS pathways. The models are humanized using data from PET, MRI, BOLD imaging, genomic datasets, and postmortem studies in both healthy and disease-specific populations. The platform is validated by simulating historical clinical trials and comparing outputs to reported outcomes.

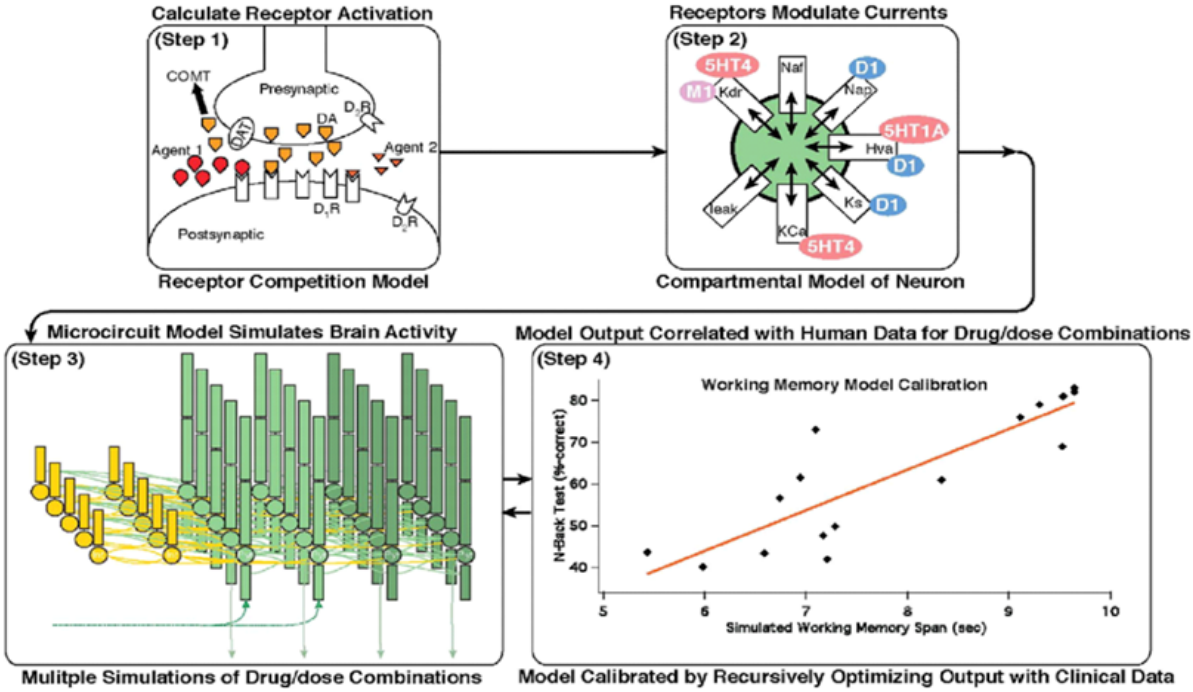

Figure 3. *(Step 1) Determine target engagement of drugs. (Step 2) Incorporate effects of targets on neuronal mechanisms such as conductance on ion channels. (Step 3) Simulate drug effects on system of neurons to determine resulting neuronal network behaviour. (Step 4) Simulate known drug clinical outcomes, modifying the effect size set in step 2 to maximize the correlation (R2) between model readout (x-axis) and clinical outcomes (y-axis).*

2.3.4.1. Functional circuits for pain, sedation, cognition, and abuse liability

To simulate pain relief, neural activity was modelled in the dorsal root ganglion, dorsal horn, rostral ventromedial medulla, periaqueductal grey, thalamus, and primary somatosensory cortex, linking it to changes in pain intensity[59].

For sedation and cognitive impairment, circuits in the prefrontal cortex have been simulated, striatum, globus pallidus externa/interna, subthalamic nucleus, and thalamus[60, 61]. Cognitive effects are linked to accuracy in a 2-back working memory task, while sedation effects are aligned with reported somnolence levels from clinical data[39].

To assess drug abuse liability, dopamine neurons and GABAergic interneurons were modelled in the ventral tegmental area, and linked outputs to "drug liking" scores[62].

2.3.5. Platform calibration and validation

To ensure reliability, the platform must be calibrated and validated against clinical data. Calibration involves adjusting model parameters to match observed outcomes from hundreds of published clinical trials on drug combinations for chronic pain. These trials provided real-world evidence on both therapeutic effects and self-reported adverse events.

Validation is a prerequisite for acceptance of any modelling platform in a clinical setting. The platform was validated by comparing its predictions for combination therapies with independent published trial results not used during calibration. Additional validation came from evoked pain studies in healthy subjects and clinical trials in post-operative pain patients, where predicted analgesic and side-effect profiles matched observed outcomes.

2.3.5.1. Predicting the effects of drug combinations

As co-medications with morphine show negligible impact on brain drug concentrations, researchers simulated drug combinations by independently combining their target effects[63]. For dose-sparing analyses, we modelled five morphine dosing regimens (0, 15, 30, 45 and 60 mg/day) combined with three regimens of over 30 augmentation drugs, across the four indications. This resulted in simulations of 450+ combinations.

For example, combining morphine 30 mg/day (10 mg dose taken 3 times per day) with duloxetine 40 mg/day (taken once per day), the PK simulations predict steady-state concentrations after four weeks. From these concentrations, we estimate morphine's binding to mu-opioid receptors in the extracellular fluid, as well as duloxetine's inhibition of serotonin and norepinephrine reuptake, leading to increased synaptic levels of both neurotransmitters. These changes in neurotransmitter availability modify receptor activation, reflecting the combined action of endogenous ligands and drug binding, which in turn alters the conductance of specific ion channels across all four models. The resulting modifications in neuronal firing are then simulated and linked to clinical outcomes.

2.3.5.2. Assessing clinical relevance through patient-centred outcomes and mechanistic insight

Beyond simulating pharmacodynamic outcomes, QSPainRelief aims to anchor its predictions in meaningful, patient-centred measures. For this purpose, we employed a Clinical Utility

Index (CUI) that balances efficacy and tolerability, aligning simulation outputs with what matters most to patients and clinicians.

Benefit-risk assessment tools are tools that weigh the benefits (e.g. desired treatment effect) against the risks (e.g. side effects). They are used by regulatory agencies in the approval process of drugs, where at the very least the benefit must outweigh the risk. In addition, a comparison is also made against already available treatments. Benefit-risk assessment tools can be classified under a quantitative and qualitative framework. A qualitative framework is a descriptive analysis of the benefits and risks. The FDA for example uses a descriptive qualitative framework in the approval process (see **Figure 4**).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

Figure 4*. FDA's Benefit-Risk Framework for New Drug Review. U.S. Food and Drug Administration.*

A quantitative framework gives a numerical value to the outcomes. An example of a quantitative framework is the CUI model that quantitatively weighs the benefits against the risks, as depicted in **Figure 5**[64]. In short, individual outcomes –such as endpoint measures over time from different doses (exposure–response relationships) and drugs – are weighted (based on their clinical importance), and if applicable, a transformation function is applied (e.g., exponential or cut-off). This leads to a clinical utility score for the different outcome measures. These scores can be used to recommend dosing regimens that provide the best efficacy/tolerability balance, aligning simulation outputs with what matters most to patients and clinicians.

$$\mathrm{CUI}_{t,d,c} = \sum_{i=1}^{n} w_i \cdot f_i(O_{i,t,d,c})$$

- **CUI** = sum of weighted functions
- **W** = weights
- **O** = outcomes
- **f** = transformation function
- **t** = time
- **d** = dose
- **C** = compound
- **i** = individual endpoint

Figure 5*. The CUI formula.*

Major advantages of a CUI model include transparency and consistency, the ability to interpolate/extrapolate across doses, easy application of alternative weights based on clinician input, patient preference or patient stratification (e.g., sex, age). It can be easily integrated with model-predicted outcomes from PKPD and QSP models.

Within the QSPainRelief platform, we integrated the QSP model predicting analgesic responses and side effects of combination treatments for chronic pain into a CUI model to predict which drug combinations are expected to benefit the patients the most.

Furthermore, we developed a proof-of-concept application in which CUI weights are elicited internally from clinician inputs. Besides clinician input, regulatory agencies encourage to include patient preferences.

Through an online patient questionnaire, we obtain data on preferences from patients with chronic pain and use this information to inform the selection of combination treatments. The questionnaire examines multiple stratifications such as pain type and severity, current side effect burden, sex and ethnicity which will help us develop the CUI model by taking patient characteristics into account, which eventually could lead to better personalized pain treatments. These patient preferences will be integrated into the weights together with those from the clinicians.

2.4. Future challenges for the use of QSP for analgesic drug development

Despite its promise, the application of QSP in chronic pain research faces some challenges. One of the most fundamental is the limited understanding of the complex and dynamic physiological processes that contribute to the chronicity of pain. Mechanisms such as peripheral and central sensitization, altered descending inhibition or facilitation, or ectopic neuronal discharges remain only partially characterized, particularly in human subjects. This knowledge gap limits the ability to fully represent pathological states within current QSP models.

Another barrier is the poor translational knowledge between animal models and human pain conditions. While QSP provides a structured framework to integrate human data, most preclinical studies still rely on simplified or acute models that do not capture the full spectrum of chronic pain phenotypes. As a result, current neural circuit models embedded in platforms

such as QSPainRelief require further refinement to simulate clinically relevant pathophysiological states.

Future developments in QSPainRelief will require the incorporation of more detailed, condition-specific mechanisms into the existing neural network models. For instance, representing maladaptive neuroplasticity, chronic inflammation, or neuropathic-like features, such as spontaneous firing or loss of inhibitory tone, will be essential for predicting drug effects in specific patient subpopulations. Integration of omics data, patient stratification biomarkers, and longitudinal clinical outcomes could further enhance the model's predictive value and personalization capacity.

Ultimately, advancing QSP for analgesic development will depend on deeper biological insights into pain chronification and more robust, human-relevant datasets to support model calibration and validation.

3. Conclusion

Chronic pain is a significant clinical and societal burden, often resistant to standard pharmacological treatments. In this complex landscape, Quantitative Systems Pharmacology (QSP) may constitute a promising approach because it can provide a mechanistic, multi-scale framework to understand and predict drug effects, from molecular interactions to patient-level outcomes.

The QSPainRelief project illustrates the potential of this approach to explore the efficacy and safety of combination treatments for chronic pain, by integrating PBPK modelling, target binding kinetics, and neural circuit simulations. The QSPainRelief platform could allow for rational drug pairing, optimization of dose regimens, and a significant reduction in the reliance on trial-and-error strategies in both preclinical and clinical settings. Critically, QSPainRelief supports a more personalized approach to treatment by accounting for individual variability in age, sex, receptor expression, and comorbidities.

Key takeaways from this work include:

- The integration of pharmacokinetics and pharmacodynamics across scales enables precise prediction of CNS target engagement and clinical outcomes.
- QSP models support the design of opioid-sparing combinations, addressing both efficacy and safety challenges in chronic pain therapy.
- The use of clinical utility indices (CUI) provides a structured benefit-risk evaluation tailored to patient-centric outcomes.

Looking ahead, QSPainRelief lays the groundwork for the broader adoption of QSP in drug development and clinical practice. Future research will focus on expanding the platform to incorporate identified pathophysiological mechanisms contributing to chronic pain, patient-reported outcomes, refine stratification methods, and strengthen model validation across diverse populations and pain conditions. By bridging mechanistic insights and clinical needs, QSP represents a key enabler for more effective, safer, and personalized chronic pain management.

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