In silico prediction of novel effective combinational treatment of chronic pain in individual patients: a joint white paper of the H2020 QSPainRelief consortium

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THEMED ISSUE REVIEW

In silico prediction of novel effective combinational treatment of chronic pain in individual patients: A joint white paper of the H2020 QSPainRelief consortium

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Abstract

Opioids are prescribed widely for chronic pain despite well-recognised risks and variable long-term benefit, reflecting the lack of effective alternatives for many patients. Combination therapies offer a promising strategy to enhance efficacy whilst reducing side effects. However, identifying effective drug combinations is notoriously difficult. The H2020 QSPainRelief project developed a model platform for in-silico prediction of efficacy and adverse effects of analgesic drug combinations, focussing

Abbreviations: ADME, absorption, distribution, metabolism, excretion; BCSFB, blood-CSF barrier; BK, binding kinetics; BOLD, blood-oxygen-level dependent; Brain ECF, brain extracellular fluid; CB1, **cannabinoid receptor 1**; CUI, clinical utility index; MOR, **mu-opioid receptor**; NSAID, non-steroidal anti-inflammatory drugs; PET, Positron Emission Tomography; P-gp, P-glycoprotein; PK-PD, Pharmacokinetics-Pharmacodynamics; THC, 9Δ-tetrahydrocannabinol; QSP, quantitative systems pharmacology; SAS, subarachnoid space; SPECT, single-photon emission computed tomography.

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on opioid–non-opioid combination strategies. It integrates physiologically-based pharmacokinetic, pharmacodynamic and neural circuit models that capture key aspects of nociceptive processing and central nervous system (CNS) side effects, and enables more advanced personalised pain management by incorporating patient-specific variables, patient-reported outcomes and patient preferences. After discussing the problem of chronic pain treatments and critical determinants of CNS drug effects, we introduce the QSPainRelief platform development and share illustrative results on prediction of morphine–non-opioid combinations effects, and inclusion of patient preferences in dealing with the side effects using a clinical utility index model. Finally, we discuss remaining gaps in data, and directions of future research to strengthen the validation and predictive performance of the platform to further support its application for the development of safer and more effective combination therapies for chronic pain. We conclude that the QSPainRelief model platform can reduce reliance on costly and slow trial-and-error methods in clinical drug development for chronic pain by bridging mechanistic insights and clinical needs, and representing a key enabler for more effective, faster, safer and personalised chronic pain management.

KEYWORDS
chronic pain, drug combinations, opioids, prediction, QSPainRelief model platform

1 | INTRODUCTION

1.1 | Chronic pain and its impact on patients and healthcare

Chronic pain, defined as pain persisting for more than 3 months, is among the most prevalent and complex medical conditions (Treede et al., 2015). It affects approximately 20% of the European population, with higher prevalence in women and older adults (Breivik et al., 2006; van Hecke et al., 2013). 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 (Elliott et al., 2003; Hadi et al., 2019). 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 (Federation, 2024; Langley, 2011). 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 (defined as a disease entity in its own right) and chronic secondary pain (in which pain occurs as a symptom of an underlying condition such as surgery- or injury-related pain) (Treede et al., 2019).

Chronic pain is a multifactorial condition shaped by biological, psychological and social factors and is best understood within a biopsychosocial framework. From a mechanistic perspective, chronic pain encompasses overlapping nociceptive (pain arising from actual or threatened damage to non-neural tissue and resulting from activation of nociceptors), neuropathic (pain arising from lesions or disease of the somatosensory nervous system) and nociplastic (pain arising from altered nociceptive processing without clear tissue damage or nerve injury) components, which may co-exist within the same patient and vary over time (Kosek et al., 2016; Treede et al., 2019). The pathophysiology of chronic pain thus involves a complex combination of genetic, physiological, neurochemical and inflammatory mechanisms (Vellucci, 2012; Yasaei et al., 2025). Peripheral and central sensitisation, together with psychological factors such as anxiety or pain catastrophising, contribute to chronicity and poor treatment outcomes (Hirsh et al., 2008; Mills et al., 2016; Simone et al., 1991; Springborg et al., 2023; Woolf, 2011). The intricate interplay between biological and psychological dimensions contributes to the challenge of effective management and highlights the limitations of current therapeutic strategies (Mills et al., 2016).

1.2 | Limited efficacy of current treatments and sources of response heterogeneity

The primary goals in chronic pain management are to reduce pain, improve function and enhance overall quality of life, whilst minimising treatment-related side effects. Current treatment strategies include both non-pharmacological and pharmacological strategies, for example, opioids, antidepressants, anticonvulsants and non-steroidal anti-inflammatory drugs (NSAIDs) (Ho et al., 2018; Lynch & Watson, 2006; Turk et al., 2011). Despite the available treatment options, about 60% of patients report insufficient pain relief, and many patients discontinue treatment due to adverse effects (Breivik et al., 2006).

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 (Bartley & Fillingim, 2013; Cook et al., 2014; Oosterman & Veldhuijzen, 2016). Importantly, this limitation does not necessarily imply that existing treatments lack efficacy at their intended physiological targets, but rather that there might often be a mismatch between the mechanisms targeted by a given treatment and the pathophysiological mechanisms present in an individual patient. Mechanism-based approaches aim to address this limitation by aligning therapeutic interventions with the dominant biological pain mechanisms present in specific patients or patient subgroups, rather than applying uniform treatments across heterogeneous populations (Soliman et al., 2024).

1.3 | Opioid-based treatments for chronic pain

Opioids present numerous clinical challenges, despite their proven efficacy in treating nociceptive and mixed pain conditions such as cancer-related pain (Cherny et al., 2001). Although they can offer relief in the acute or subacute setting, the available evidence fails to demonstrate sustained benefit over periods of a year or more. Long-term opioid therapy is associated with significant risks, including the development of tolerance (requiring escalating doses for the same effect), physical dependence and opioid use disorder. Moreover, opioids may induce relevant side effects such as sedation, cognitive impairment, constipation and respiratory depression, which can severely impact patients' quality of life and limit treatment adherence (Hirsh et al., 2008). These complications are especially concerning for chronic pain populations, where extended treatment durations increase the likelihood of adverse outcomes (Hirsh et al., 2008). A notable 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 (Hanks et al., 1996). Furthermore, long-term opioid use is strongly linked to dependence and misuse risk, as dramatically illustrated by the opioid crisis in the United States where widespread prescription of opioid analgesics has contributed to high rates of misuse, addiction and opioid-related mortality (Brady et al., 2016). This situation highlights the potential consequences of prolonged opioid exposure even under medical supervision, making the development of safer and more effective treatment regimens a public health imperative. Agencies such as the CDC and FDA advocate stricter prescribing guidelines, enhanced monitoring and the prioritisation of non-opioid therapies.

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 (Waisundara et al., 2021). Many agents also impair mobility, memory and physical activity, key determinants of function and quality of life (Zakka et al., 2024). The development of new analgesics remains slow and uncertain. Although there have been a few incremental innovations and recent approvals, no broadly transformative new class for chronic, noncancer pain has been widely adopted in decades. The overall clinical development-to-regulatory approval success rate for central nervous system (CNS)-active drugs is approximately 14%, based on aggregated historical analyses of drug development outcomes across major regulatory jurisdictions, and is lower than the average success rate of approximately 20% observed across all therapeutic areas (Barakat et al., 2024).

Given these limitations, combination pharmacotherapy has emerged as a promising strategy. Formally described in the 1980s and popularised by Kehlet and Dahl, combination pharmacotherapy or 'multimodal analgesia' is recommended when monotherapy provides only partial or inadequate relief (Kehlet & Dahl, 1993). 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 (Breitinger & Breitinger, 2023). Treatments like opioids enhance inhibition, whereas drugs such as **gabapentin** or **pregabalin** reduce excitation (Chincholkar, 2018; Martel et al., 2019). Rational combination approaches therefore aim to act synergistically—for example, by targeting both peripheral and central mechanisms to block transmission and modulate central processing. Frequently used combinations include **paracetamol** with opioids, NSAIDs with opioids, muscle relaxants with opioids and various antidepressant-anticonvulsant pairings (Boccella et al., 2023; Chaparro et al., 2012).

1.5 | Conventional analgesic drug development

In conventional analgesic drug development, empirical correlations between drug exposure and clinical pain scores are usually characterised 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 personalised treatment, these models may 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 (De Lange, 2013a, 2013b).

1.6 | Lack of rigorous clinical trials evaluating analgesic combinations

As indicated above, the development of new analgesics remains slow and uncertain (Barakat et al., 2024). Combination therapies have been proposed, but rigorous clinical trials assessing these combinations remain scarce, and there is an urgent need for systematic, mechanism-based approaches to identify, assess and personalise combination therapies—ultimately aiming for more effective and tailored chronic pain management.

Several structured reviews and systematic meta-analyses have summarised the available clinical evidence on pharmacological combination therapies for chronic pain involving antidepressants, anticonvulsants, opioids and other CNS-acting drugs, with a particular focus on neuropathic pain conditions (Balanaser et al., 2023; Boccella et al., 2023; Chaparro et al., 2012; Serrano Afonso et al., 2021). Collectively, these analyses highlight both the potential benefits of specific combinations—some of which may improve analgesic efficacy or tolerability compared to monotherapy—and the substantial limitations of the existing literature. These limitations include heterogeneous study designs, limited sample sizes, variable outcome measures and definitions of treatment response, inconsistent endpoints that complicate cross-study comparisons and insufficient consideration of adverse effects and overall benefit–risk balance. Importantly, these reviews also emphasise that many clinically relevant pharmacological strategies have been explored empirically, without a unified framework enabling systematic comparison across drug classes, doses and patient populations.

Available evidence for the effectiveness of treatment combinations remains limited and variable. Whereas some pairings outperform their individual components, others do not, endorsing the importance of combination-specific research (Hanks et al., 1996). Many clinical trials have not been designed to disentangle individual contributions of each drug within a combination, limiting the ability to draw robust conclusions regarding additive or synergistic effects (Chaparro et al., 2012). Focusing on the specific case of opioid–non-opioid combinations, some studies comparing opioid monotherapy with opioid–non-opioid combination therapy have provided insights into optimising pain management strategies (Li, 2019). Some reviews suggest that combining opioids with non-opioid analgesics, such as NSAIDs or paracetamol, can enhance analgesic efficacy whilst reducing the required opioid dose, thereby mitigating associated risks such as tolerance, dependence and adverse effects (Carter et al., 2020; Li, 2019; Santini et al., 2017).

In summary, combination therapies represent a promising strategy to improve analgesic efficacy whilst reducing treatment-related risks in chronic pain. However, the complexity and multiplicity of pain mechanisms, substantial inter-individual heterogeneity even across similar primary or secondary chronic pain conditions and the large number of potential drug targets, dose regimens and drug–drug interactions generate a combinatorial therapeutic space that cannot be exhaustively explored through conventional empirical testing alone. Existing pharmacological modelling approaches in this area often address either drug exposure or pharmacodynamic effects in isolation and rarely integrate physiologically based descriptions of CNS drug exposure with interacting pain mechanisms, patient variability and the concurrent emergence of both desired therapeutic effects and undesired CNS side effects such as sedation. As a result, there remains a clear gap for integrative, mechanism-based frameworks capable of jointly evaluating efficacy–safety trade-offs across candidate combination treatments.

2 | COMPLEXITY IN THE RELATION BETWEEN DRUG DOSING AND CNS EFFECTS

The CNS is an organ with complex anatomy, structure and function. In many tissues in the body, a drug is relatively free to exchange between blood and the extracellular space in the tissues, but this is not the case for CNS tissue. The CNS is separated from the blood by the blood–brain barrier (BBB) and other barriers that have highly specialised properties (Abbott et al., 2010), which can lead to large differences between drug exposure in plasma versus the CNS.

The CNS is far from being a homogenous tissue, with many different tissue structures and fluid cavities (ventricles), and target expression may vary substantially among the different locations (Sawada et al. 1991). The same drug target receptor may have distinct functions in different locations of the CNS. Finally, fluid production and flow rates in the CNS, that is, of the cerebrospinal fluid (CSF) and brain extracellular fluid (brain ECF), lead to complex and spatially varying patterns of drug disposition in the CNS (De Lange, 2013a, 2013b; De Lange et al., 2017).

CNS functionality is complicated by the networks of interacting neurotransmission pathways. Neurotransmitter receptors have been the typical target for many (classical) CNS drugs, whereas 'single target' pharmacological intervention and/or the impact of a disease on one target will often influence another one. Thereby, CNS effects often are not directly quantifiable and need to be assessed in an indirect way by using biomarkers that may adequately reflect the real CNS effect. Neuroimaging methods can be of particular value because they can provide non-invasive, objective and longitudinal in vivo measures of CNS function and target engagement. Modalities such as PET, SPECT and functional MRI have been used in both animals and humans that support translation (Borsook et al., 2013; Evangeline & Darwin, 2026). Still, CNS drug effects, especially for treating (chronic) pain conditions, are difficult to measure and predict.

These considerations all indicate that the relationship between drug dosing and the ultimate CNS effect(s) is complex and that we should have knowledge about plasma PK and (protein) binding, cerebral blood flow, BBB functionality, brain tissue binding, target site PK, receptor-drug binding kinetics and signal transduction to the effect, which are interrelated and condition dependent (De Lange, 2013a). Figure 1 shows a general overview of all the steps between drug dosing and effect.

Because information on CNS drug distribution in human brain typically cannot be obtained directly, it must be inferred from in vitro and in vivo preclinical experimental data and in silico approaches. In this, there still is a reductionist tendency to oversimplify the relevant factors underlying CNS drug effects wherein key contributing factors are often evaluated only in isolation, neglecting the complex interactions and interrelationships, whilst not specifically addressing the

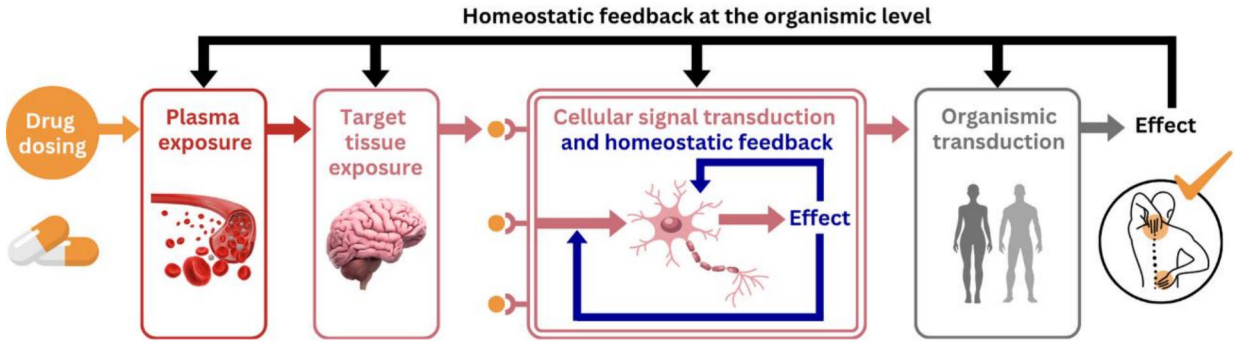

FIGURE 1 The relationship between drug dosing and the ultimate effect is complex. It involves multiple processes, being interrelated and condition dependent. The effect is ultimately dependent on the drug dose, plasma PK, CNS target site distribution, target binding kinetics, cellular response and homeostatic feedback at the cellular level and body response and homeostatic feedback at the organismic level.

context dependency of these values. Such 'fragmented' and 'stand-alone' data do not lead to increased understanding. As such, there is a need to understand multiple processes, and their inter-relationships and condition dependencies in a systematic manner (de Lange et al., 2005; De Lange, 2013a).

2.1 | CNS drug distribution

CNS drug distribution from plasma to the target site is governed by multiple factors, including the bidirectional transport of unbound drug molecules across CNS barriers and their subsequent distribution within brain compartments.

2.1.1 | Plasma PK

The concentration-time profile of unbound drug in plasma is a key determinant of transport across brain barriers. Neutral unbound drug molecules can diffuse through the cell membrane of brain barrier structures whereas all unbound molecules—if sufficiently small—can cross between the barrier cells.

2.1.2 | Transport across the BBB and BCSFB

The BBB and blood-CSF barrier (BCSFB) regulate the movement of drugs into and out of the CNS. Although structurally distinct, formed by endothelial cells for the BBB and by choroid plexus epithelial cells for the BCSFB, both regulate transport based on drug 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. Only unbound and sufficiently small or lipophilic drugs can cross membranes in this way. For hydrophilic drugs, movement is strongly restricted by tight junctions, limiting paracellular transport across the BBB.
- *Facilitated diffusion*, also passive but saturable, this process requires specific transporter proteins to carry drug molecules across barrier membranes.
- *Fluid Phase (vesicular) transport* includes pinocytosis, adsorptive-mediated endocytosis and receptor-mediated endocytosis. Although 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 in the cells 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. 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.

2.1.3 | 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, whereas the transport of less permeable drugs remains largely unchanged. Variations in capillary perfusion, the 'effective perfusion', can affect BBB transport for all drugs.

2.1.4 | 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*. 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 for drugs with a slow distribution into the CSF. Brain ECF fluid comes from the BBB, and brain ECF bulk flow may reduce brain ECF drug concentrations for drugs that slowly pass the BBB.
- *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 optimising therapeutic effects.
- *Drug metabolism*. Metabolic activity within the CNS also may reduce CNS drug concentrations. Drug metabolising enzymes (DMEs) present in the BBB, BCSFB and ependymal cells may act as barriers, metabolising drugs before they enter the brain. Additionally, brain cells may contain DMEs.

It is of great importance to understand CNS distribution of the unbound drug, because it drives drug-target binding (Watson et al., 2009).

2.2 | Drug target binding

Drug-target binding, the interaction between a drug and its intended biological target, induces signal transduction processes which ultimately lead to a biological effect. This is a complex process influenced by various factors that include drug and target characteristics.

2.2.1 | Drug properties and drug concentration

- *Molecular structure*. A drug's size, shape and functional groups, critically influence its ability to bind with target proteins. Lipophilic drugs tend to bind more readily to proteins.
- *Equilibrium binding rate constant*. Often denoted as *K*, it represents the ratio of association (K_{on}) and dissociation (K_{off}) rate constants in a reversible binding reaction between a molecule (ligand) and its binding partner (protein or receptor). It indicates the strength of the interaction, with a higher *K* signifying a stronger interaction.
- *Drug concentration*. Increasing drug concentration generally leads to increased binding to the target, up to a saturation point where all target binding sites are occupied.

2.2.2 | Target characteristics

- *Target protein structure*. The three-dimensional conformation of the target, including the presence of specific binding pockets, is a major determinant of binding.
- *Binding site properties*. The size, shape, hydrophobicity and electrostatic potential of the binding site influence which drugs can bind.
- *Conformational changes*. Some targets undergo conformational changes upon binding, which can affect the stability and duration of the drug-target complex.
- *Target activatability*. Some targets are more sensitive to drug binding than others, requiring different levels of target occupancy to achieve a desired therapeutic effect.
- *Target expression/concentration*. The concentration of the target protein in the body can affect the overall binding capacity.

2.2.3 | Drug-target binding kinetics

Factors such as the speed of binding (on-rate) and unbinding (off-rate) can affect how long a drug stays bound to its target and influence its overall effect, especially in cases of 'rebinding' where the drug diffuses back to the target site. Moreover, additional factors such as target turnover/desensitisation, endogenous ligand binding/competition and signal transduction can influence the time course of drug action and need to be considered (De Witte et al., 2016).

2.3 | Receptor activation, signal transduction and CNS drug effects

CNS drug effects are mediated through receptor activation and subsequent signal transduction pathways. These pathways involve a series of intracellular events triggered by the binding of a drug to its target receptor, ultimately leading to changes in neuronal function and behaviour.

2.3.1 | Receptor activation

Just like endogenous signalling molecules, drugs interact with specific receptors on or within cells to initiate a response. These receptors, often transmembrane proteins, bind to the drug (ligand) and undergo a conformational change, which activates the receptor. Different types of receptors mediate various CNS effects. Types of receptors include the following:

- *G-protein coupled receptors (GPCRs)*. Binding of drugs to these receptors activates G-proteins, which in turn influence intracellular signalling pathways. Once engaged by agonists, a GPCR may recruit nonvisual arrestins that function as molecular scaffolds, activating further components of intracellular signalling and influencing receptor trafficking (and thus GPCR levels on cell surface).
- *Ion channels:* Drugs can directly modulate ion conductance across cell membranes, altering neuronal excitability.
- *Enzymes:* Some drugs act as enzyme inhibitors or activators, affecting cellular processes.

2.3.2 | Signal transduction

The activated receptor triggers a cascade of intracellular events known as signal transduction. This process involves a series of molecular interactions, including the activation of enzymes, changes in ion channel activity and alterations in gene expression. These pathways can regulate neuronal excitability, synaptic transmission and neuronal survival, ultimately influencing behaviour.

2.3.3 | Neuronal excitability and synaptic transmission

Drugs can significantly alter neuronal excitability and synaptic transmission in the brain, impacting various functions like mood, awareness and behaviour. These effects can be achieved by directly mimicking neurotransmitters, interfering with their release, reuptake or receptor binding or by altering the molecular components of the synapse.

Altogether, to achieve a meaningful CNS effect, a drug should have the ability to access the CNS '*at the right place, at the right time, and at the right concentration*'. For the development of treatments with improved CNS effects, one of the scientific challenges is to understand the biological mechanisms underlying the PK-PD relationships of CNS drugs. The currently applied simplistic approach to producing data on multiple processes in isolation is not informative because processes are context dependent and interdependent. Acquired knowledge on heterogeneity (variability) in rate and extent of processes between drug dosing and CNS effects is needed to predict the impact of drug-induced and disease-induced perturbations in the biological system. To that end, an integrative 'Mastermind Research Approach' is needed to decipher the inter-relationships of processes that govern CNS drug effects in different conditions. To that end, mathematical models are needed (De Lange, 2013a; De Lange et al., 2017).

3 | A QUANTITATIVE SYSTEMS PHARMACOLOGY (QSP) MODEL-DRIVEN APPROACH TO OPTIMISE COMBINATION TREATMENTS

Building on the multiplicity and combinatorial complexity outlined above, the sheer number of possible drug and drug-dose combinations presents a major practical challenge due to constraints in time, cost and feasibility. For example, testing just three doses of an opioid with three doses of one of 20 drugs that could be used in the combination to potentially improve the effects ('augmentation drugs') would already require 180 combinations. Including multiple opioids, more augmentation drugs and accounting for patient characteristics such as age, sex or pain aetiology increases this number exponentially. Exhaustive exploration through animal studies or clinical trials therefore quickly becomes unfeasible.

One way to address this challenge is through in silico models based on 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. By integrating pharmacology with systems biology, QSP can mechanistically link drug exposure to both therapeutic and adverse outcomes in a quantitative and predictive manner. QSP models can link drug dosing to time-dependent (unbound) brain concentrations, target engagement and downstream physiological and behavioural effects. Physiologically based pharmacokinetic (PBPK) models predict how drugs are absorbed, distributed, metabolised and excreted (ADME), as well as how they distribute into and within, for example, the CNS, and the PK at CNS target sites. This can be used as input for target binding kinetic (BK) models that provide receptor occupancy over time—which subsequently are fed into spiking neuronal network models to simulate system-level outcomes including analgesia, sedation, cognitive impairment and abuse liability.

Such a QSP model approach relies on dynamic, mechanism-based modelling to build realistic, knowledge-based simulation platforms (Jones & Rowland-Yeo, 2013). 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 (Ingólfsson et al., 2023; Verma et al., 2026). By leveraging these multiscale models, researchers can simulate and predict potential clinical outcomes in silico and generate mechanistically informed hypotheses that can be tested, significantly accelerating and focusing experimental efforts (Ingólfsson et al., 2023).

The complete characterisation of pain and its pharmacological, physiological and psychological processes may be possible by using QSP approaches (Danhof, 2016; De Lange et al., 2017; Goulooze et al., 2017). QSP models have improved properties for translation and prediction because 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. Thereby QSP models have a strong 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 (Barakat et al., 2024).

In the context of CNS-active drugs, a range of modelling approaches have been developed to capture different aspects of drug action, including physiologically based pharmacokinetics (PBPK) models to predict CNS exposure, (plasma) pharmacokinetics/pharmacodynamic (PK/PD) models describing exposure–response relationships, binding kinetic models that predict drug-target binding and neural network models, to simulate drug action on the dynamics of neural systems. Unique examples of successfully developed QSP models integrating receptor occupancies of CNS-active drugs and the neurotransmitter pathway dynamics to predict drug responses, are the ones for Alzheimer's disease (Roberts et al., 2012) and schizophrenia (Geerts et al., 2013).

QSP model approaches in pain research and treatment have so far remained relatively limited. These include a systems biology model on **nerve growth factor** signalling axis, which plays a key role in chronic pain and has been explored to support target identification and validation (Toni et al., 2014), and a whole body PBPK-informed QSP model applied to pain-relevant inflammatory pathways (Thiel et al., 2018). Whereas these approaches provide valuable insights, they do not explicitly link CNS target engagement to system-level neural dynamics, clinical analgesic efficacy and adverse CNS effects within a unified framework.

An integrated CNS PBPK based QSP model framework on pain relief would provide a basis for exploring how inter-individual variability and mechanism-specific alterations in nociceptive processing contribute to variable treatment responses. This approach would support more mechanism-based patient stratification and rational selection of drug treatments or treatment combinations. This approach also would allow the use of a plethora of drugs already clinically used. At the same time, limited commercial incentives constrain the conduct of new large-scale clinical trials of combinations of existing (off patent) drugs.

4 | THE QSPAINRELIEF PROJECT

QSPainRelief was a European H2020-funded research consortium project (grant agreement No 848068, 2020–2025). The key objective of the QSPainRelief consortium ('QSPainRelief') project was to develop the QSPainRelief model platform, as an in-silico simulation platform capable of predicting the effects of novel CNS-active drug combinations in individual patients, with a specific focus on opioid–non-opioid combinations (Geerts et al., 2013; De Lange, 2013a; Danhof, 2016; Goulooze et al., 2017; van Hasselt & Iyengar, 2019). With that objective, QSPainRelief aimed 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. To that end, QSPainRelief brought together expertise from academia, industry, clinical practice and patient organisations. By integrating patient-specific factors such as age, sex and psychosocial traits, the platform was designed to support a personalised medicine approach, tailoring treatment combinations to maximise efficacy whilst reducing adverse effects.

To develop such an integrated multiscale QSP approach for analgesic drug development, the QSPainRelief project was structured around a set of interconnected work packages covering platform development, data generation and validation (Figure 2 and Table 1). These packages included the development of CNS pharmacokinetic models (Gülave et al., 2023; Gülave, Lesmana, et al., 2025; Gülave, van den Maagdenberg, et al. 2025), drug–target binding (Budda et al., 2024, 2025; Renault & Giraldo, 2021; Ricarte et al., 2021) and signalling models, and biophysically grounded neural circuit models capturing key aspects of nociceptive processing, sedation, cognition and drug abuse liability. These modelling efforts were complemented by in vitro (Cuna,

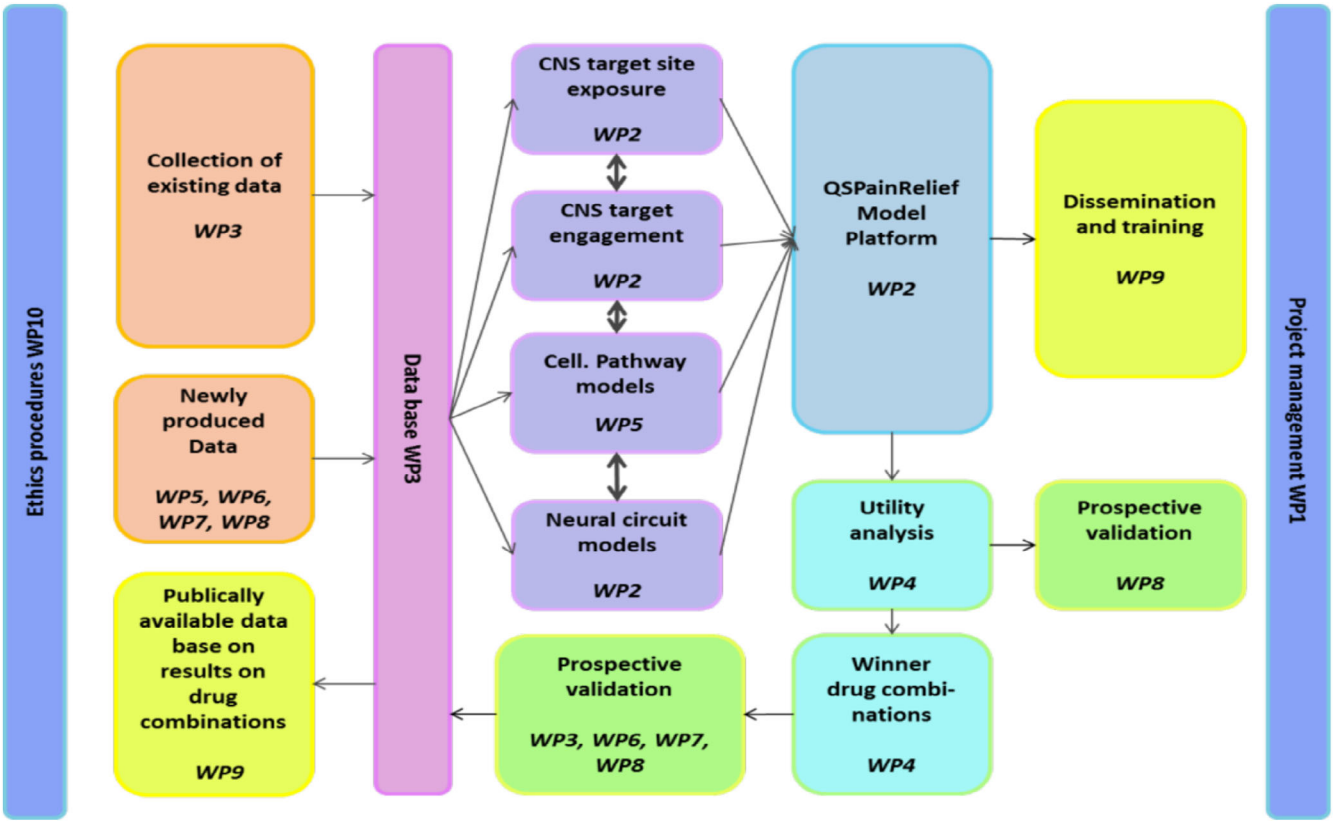

FIGURE 2 The QSPainRelief work packages, their main contributions and their interactions.

TABLE 1 Collection of existing data included the following data categories and types (* for explanation on abbreviations and meaning; see de Lange & Hammarlund-Udenaes, 2015), and drugs.

Data category	Types
Species	Human, rat, mouse
Gender	Male, female
Age	Young, adult, old
Condition	Healthy, chronic pain
Drug physico-chemical properties	Lipophilicity, molecular weight, pK_a, pK_b, etc.
Pharmacokinetics	Plasma, brain, fu plasma, fu brain, csf lv, csf cm, csf sas, kpuu bbb, kpuu bcsfb, kpuu brain cell, kpuu brain lysozymes, kp brain (*)
Target expression	Receptors, channels
CNS region	Cortex, dendate gyrus, striatum, dorsal horn
Drug target binding kinetics	Affinities, on rates and off rates to receptors, channels
Brain/neural imaging	Functional magnetic resonance imaging (fMRI), positron emission tomography (PET)
Drug class	**Drug**
Opioids	Morphine, oxycodone, naloxone, fentanyl, hydrocodone, codeine, tramadol, methadone, hydromorphone, meperidine, buprenorphine, alfentanil, tapentadol, sufentanil and alfentanil
NSAIDs	Acetaminophen, ibuprofen, naproxen, diclofenac, celecoxib, aspirin
CB_1 analgesics	THC, cannabigerol, drinabant, ibipinabant, otenabant, pregnenolone, rimonabant, rosonabant, surinabant, taranabant, tetrahydrocannabivarin, virodhamine
Benzodiazepines	Diazepam, alprazolam, clonazepam, midazolam
Anti-epileptics	Gabapentin and pregabalin
SSRIs	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, viibryd
SNRIs	Desvenlafaxine, duloxetine, milnacipran, venlafaxine
MAO-Is	Isocarboxazid, phenelzine, tranylcypromine
Tricyclic antidepressants	Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine
Miscellaneous	Bupropion, buspirone, maprotiline, mirtazapine, reboxetine, trazodone, vilazodone

2025), preclinical PK-PD studies in animal models of neuropathic pain and drug abuse liability (Cabañero et al., 2022), experimental PK-PD studies in healthy volunteers using neurophysiological and behavioural biomarkers (Bakker et al., 2025), prospective clinical studies (Gousset, 2025; Gousset et al., 2025; Rinaudo et al., 2025) in patients with chronic pain and clinical utility index (CUI) models. This structure enabled iterative integration and evaluation of model components across biological scales, from drug exposure and target engagement to neural dynamics and clinical outcomes.

5 | THE QSPAINRELIEF MODEL PLATFORM- INTEGRATING PBPK, BK AND QSP MODELS

5.1 | PBPK, BK and QSP model characteristics

The QSPainRelief model platform is an assembly of PBPK, BK and QSP models. Each model component feeds into the next, in the order listed, to enable one to go from drug/dose inputs eventually to neurological results which are linked to clinical outcomes. Their general characteristics are described below.

PBPK models represent the organism as interconnected compartments (e.g., liver, kidney and brain) and simulate ADME processes using physiological flows and anatomical features (Honório et al., 2013). By incorporating detailed individual biological parameters, they can account for inter-individual variability, including species, age, sex, genetics and disease states (Rostami-Hodjegan, 2012). This mechanistic foundation makes PBPK models highly relevant for translating animal or in vitro data to humans (Jones & Rowland-Yeo, 2013). Typical PBPK inputs include the following:

- *Drug-specific parameters:* Key molecular properties such as molecular weight (MW), ionisation constants pK_a/pK_b, lipophilicity (LogP), polar surface area and H-bond donors/acceptors.
- *System-specific parameters:* Physiological factors such as compartment volume, blood and other fluid flows, membrane properties, surfaces and pH.
- *Biological parameters*: Factors such as plasma protein binding, tissue binding, enzyme affinities, transporter affinities and receptor affinities.
- *Kinetic parameters:* absorption rates, elimination constants and enzyme and transporter kinetics with, for example, Michaelis–Menten parameters.

Together, these parameters determine drug kinetics at the compartmental level and are thus essential to predict CNS exposure (Kuepfer et al., 2016).

BK models describe the rates at which drug molecules associate with and dissociate from their specific biological targets, such as proteins or receptors (De Witte et al., 2017; Knockenhauer & Copeland, 2024). They use the following:

- Unbound drug target exposure
- *Association rate constants* (k_{on}): The speed at which a drug binds to its target.
- *Dissociation rate constants* (k_{off}): The speed at which a drug detaches from its target.
- Target expression in relevant physiological compartments to determine how and where drugs engage with their targets and provide as output:
- *Target occupancy:* The fraction of target molecules bound by the drug at a given time.

- *Residence time* (RT): The average time a drug remains bound to its target, calculated as $1/k_{off}$.
- *Target vulnerability*: The relationship between target occupancy and the desired therapeutic effect.

These models are crucial for understanding how long a drug remains bound and how effectively it interacts with its target, influencing its duration of action and overall therapeutic effect.

QSP neural circuit models address system-level effects like cellular feedback or disease dynamics, that is, 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 (Danhof, 2016; Geerts et al., 2016; Joshi et al., 2023). QSP emphasises the importance of considering the interconnectedness of different biological systems and how a drug's effects can cascade through these systems. 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 (Geerts et al., 2012; Geerts et al., 2013).

5.2 | The QSPainRelief model platform

The QSPainRelief platform integrates the CNS PBPK model (LeiCNS-PK3.0), the BK models and the QSP neural circuit models covering analgesia, sedation, cognition and abuse liability. These models require target occupancy data, which depend on target-site exposure, target expression and drug-target binding kinetics (Figure 3). As the core opioid, morphine has been chosen.

5.2.1 | The LeiCNS PBPK model

Physiological CNS compartments include the brain microvascular space (brain MV), brain extracellular fluid (brain ECF), brain intracellular fluid (brain ICF) and several CSF spaces. CNS drug distribution depends on physiological fluid flows, passive and active transport across the BBB and BCSFB, extracellular–intracellular exchange and pH gradients. Physiological fluid flows include cerebral blood flow (CBF), brain ECF bulk flow and CSF flow (Westerhout et al., 2012). The LeiCNS-PK3.0 model includes all these aspects and is currently the most comprehensive CNS PBPK model available. It includes compartments for the brain microvasculature, BBB, BCSFB, brain ECF, brain cells, subcellular lysosomes and CSF in lateral ventricles, third and fourth ventricles, cisterna magna and subarachnoid space (Saleh et al., 2021, 2023).

This model captures both bound/unbound and ionised/unionised 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. The LeiCNS PBPK 3.0 model predictions are shown for limited human data available for a few drugs (Figure 4), with predictions being within two-fold error of observed data in humans from other studies. 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 is used to predict CNS target site exposure (PK profiles) at relevant target sites (De Lange, 2013b; Gülave et al., 2023).

For morphine, as our core opioid, the generic comprehensive LeiCNS-PK3.0 model was further refined to incorporate morphine-specific BBB transport processes, including those for its active metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), thereby enabling a more accurate assessment of morphine CNS exposure relative to total metabolite contributions (Gülave et al., 2023). This assessment was done for clinically relevant dosing regimens of morphine based on intravenous, oral immediate- and extended-release formulations. The ratio between brain ECF and unbound plasma concentrations at steady state (Kpuu,BBB), being the ratio of unbound drug concentrations in brain ECF and plasma at steady-state (De Lange & Hammarlund Udenaes, 2022), is an important input parameter in the LeiCNS PBPK model. The nonlinear morphine BBB transport leads to a plasma concentration-dependent Kpuu,BBB value, being more pronounced in low-dosing regimens, affects the concentration ratios between morphine and its metabolites at the target pain matrix sites.

As Kp,uu, BBB values for may drugs are unavailable, a quantitative drug structure–property relationship (QSPR) model was developed to predict rat Kp,uu, BBB values. Rat Kp,uu, BBB values were obtained for 98 compounds, from literature or in house historical data. Among all machine learning algorithms, a random forest best predicts Kp,uu, BBB. The obtained rat Kp,uu, BBB were successfully integrated

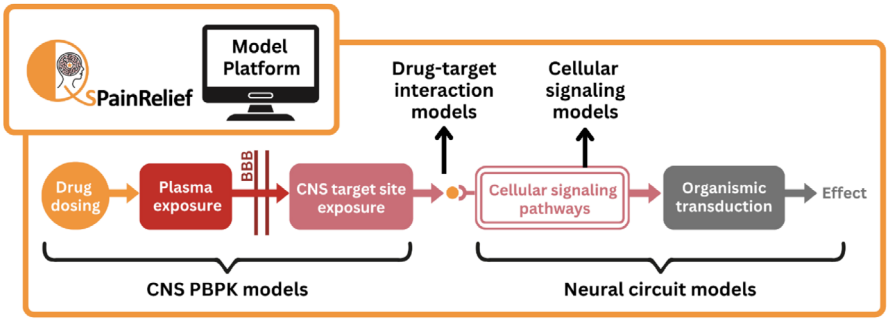

FIGURE 3 The QSPainRelief model platform assembles the LeiCNS PBPK model, the drug-target binding kinetic model and the Quantitative Systems Pharmacology (QSP) neural circuit models to predict central nervous system (CNS) drug effects.

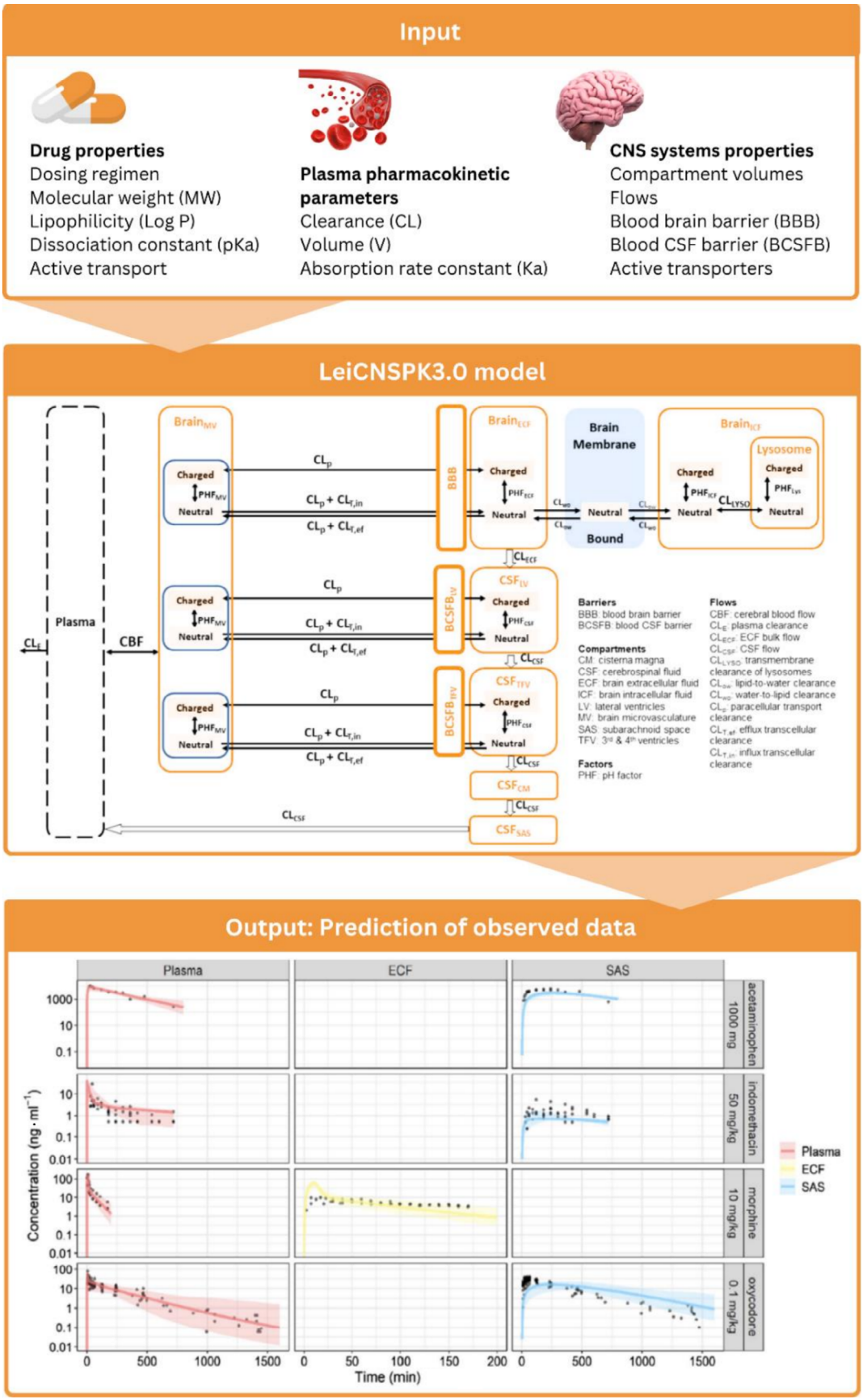

FIGURE 4 Legend on next page.

into the LeiCNS-PK3.0 CNS PBPK model (Gülave, van den Maagdenberg, et al. 2025) and translated to human, based on relative BBB transporter expression.

As an alternative approach, we investigated whether in vitro apparent permeability (P_{app}) and corrected efflux ratio (ER_c) extracted from literature could be repurposed as input for the LeiCNS-PBPK model to confidently predict rat brain extracellular fluid (ECF) PK of P-glycoprotein (P-gp) substrates (in vitro in vivo extrapolation, IVIVE). This was done for multiple drugs and multiple cell lines. It was found that accurate rat brain ECF PK predictions of passively diffusing drugs is possible. However, important mechanistic information about the relationship between P-gp expression and functionality appears to be missing for robust scaling of P-gp activity at the BBB (Van Valkengoed et al., 2025). This, in combination with conflicting information of the commonly used assumption on a linear relationship between transporter expression and activity, has led to applying a mechanistic model on P-gp expression-activity relationships. Here, we showed that P-gp expression is not always proportional to P-gp activity. Simulation-based assessment of the P-glycoprotein expression-activity relationship showed a drug and system dependency, and the ratio of the transporter-drug dissociation rate constant and efflux rate constant (k_{off}/k_e) of a drug was found to be an important determinant of this relationship (Van Valkengoed et al., 2026).

5.2.2 | The LeiCNS BK model

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. The LeiCNS 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 brain extracellular fluid (brain ECF) and subarachnoid space (SAS) derived from PBPK outputs. Combining these with receptor affinities and MOR expression levels across brain regions, we calculated the regional fraction of occupied receptors.

For morphine, our core opioid, the regional CNS exposure profiles for morphine, M3G and M6G for clinically relevant dosing regimens (Gülave et al., 2023) were used as input for the LeiCNSBK models. In the LeiCNSBK model, these PK profiles were combined with MOR expression and morphine and metabolites binding kinetic parameters (k_{on} and k_{off}) to derive corresponding MOR occupancies at multiple CNS pain matrix locations. This resulted in substantially different relative MOR occupancies between different dose regimens, formulations and CNS locations (Budda et al., 2024). At lower doses, morphine dominated MOR occupancy in multiple pain matrix areas (i.e., cerebral cortex, thalamus, midbrain, pons and medulla oblongata) driven by non-linear BBB transport. At higher concentrations, M6G contributed to higher MOR occupancy than morphine, driven by higher binding affinity, whereas M3G MOR occupancy was lowest throughout all doses. Also, formulation and administration route showed differences in these MOR occupancy profiles. These findings show how non-linear BBB transport effect translates from CNS target site concentrations to different MOR occupancy profiles in pain matrix regions (Figure 5). These observations further indicate that plasma PK profiles alone are not sufficient, and even CNS target site PK profiles can differ from the MOR occupancies, and thus possibly explain inter-individual differences observed in analgesia. Together, these results show that an integrated approach for CNS PBPK-BK may offer a more mechanistic step towards accurate prediction of MOR occupancy for morphine, with translational potential for other CNS-active drugs (Budda et al., 2024).

The LeiCNS BK model was further extended with competitive binding kinetic modules for morphine with endogenous opioids **leu-enkephalin**, **met-enkephalin**, **endomorphin-2**, **dynorphin A 1-11** and **β-endorphin** in the rat hypothalamus. Finally, the fully integrated PBPK-binding kinetic (PBPK-BK) framework incorporating inter-individual variability in plasma pharmacokinetics, CNS distribution and receptor-related processes was validated against positron emission tomography (PET)-derived receptor occupancy data for **dopamine D_2 receptor** ligands in healthy humans and patients with schizophrenia (Budda et al., 2025).

Furthermore, for dopaminergic, serotonergic, noradrenergic and muscarinic receptors, a mathematical generic synapse model was used (Spiros et al., 2010). 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** and **serotonin** [5-HT]), 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 heteromerisation (i.e., 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 (Fujita et al., 2014; Gomes et al., 2013; Ugur et al., 2018).

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

FIGURE 4 The LeiCNSPK3.0 physiologically based pharmacokinetic (PBPK) model uses central nervous system (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 humans (and for mice and rats; not shown here).

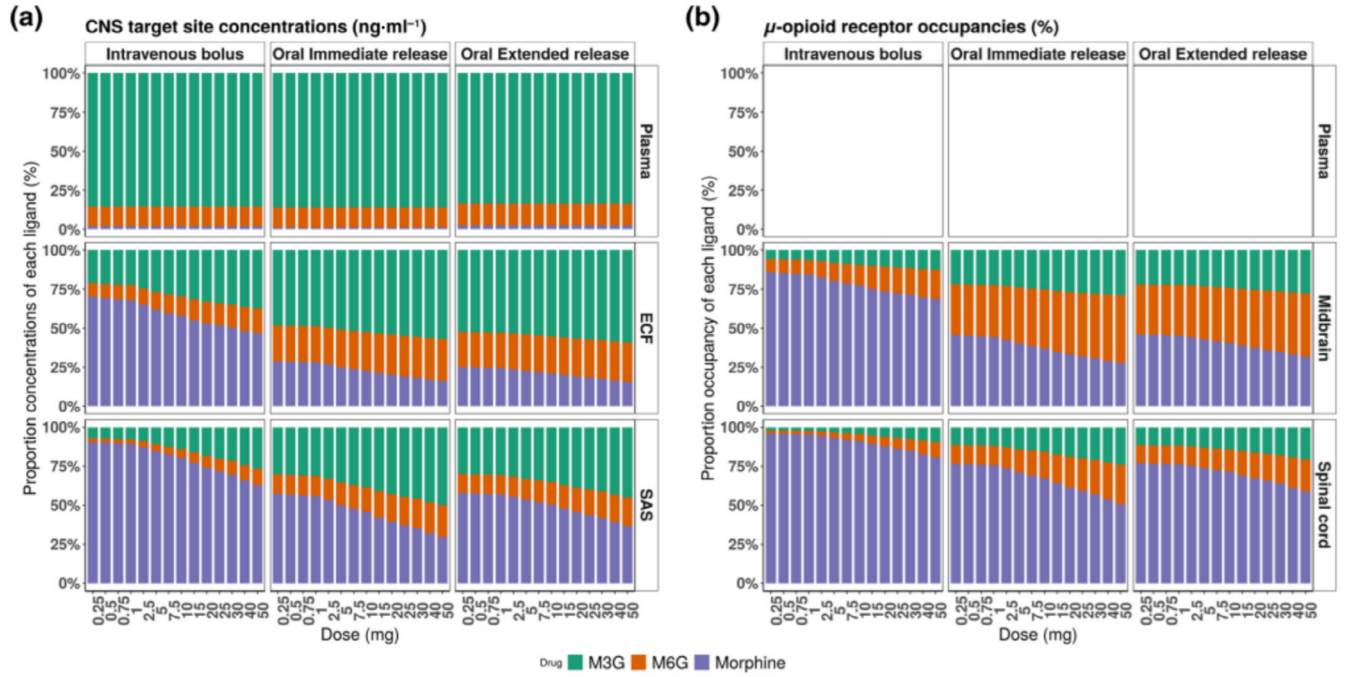

FIGURE 5 Morphine, M3G and M6G: (a) Relative plasma, brain extracellular fluid (brain ECF) and cerebrospinal fluid–subarachnoid space (SAS) concentration fractions. (b) Corresponding MOR occupancy fractions in midbrain and spinal cord, for once daily dosing regimens and formulations. (Budda et al., 2024).

- 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 (Ortiz et al., 2024; Díaz et al., 2023), and including the quantification of the residence time of the drug combination (Ortiz et al., 2025).
- A *structural modelling approach*, using coarse-grained molecular dynamics simulations to investigate the self-assembly of MOR, **DOR** and **KOR** opioid receptors with the cannabinoid **CB_1 receptor**. The coarse-grained simulations led to the identification of the most probable dimer interfaces. However, due to their inherent limitations, these simplified models did not include ligands and did not allow the study of large-scale conformational changes. To investigate the effect of ligands, the heterodimer models identified in the coarse-grained trajectories were converted to all-atom representation and subjected to molecular dynamics simulations. The dimeric configurations were then analysed in terms of receptor-receptor interactions, as well as the interactions between MOR and CB_1 with morphine and **THC**, respectively. Moreover, the predicted MOR-CB_1 dimer interfaces were experimentally validated via in vitro analysis of receptor co-localisation in cells expressing combinations of either wild-type receptors or receptors specifically mutated in those amino acids predicted to be relevant for receptor heteromerisation (Cuna, 2025; Renault et al., submitted to Communication Biology). Within the same in vitro experimental setting as described above, morphine and THC effects on receptor heteromerisation and intracellular signalling were investigated; this approach allowed us to obtain information and quantitative pharmacological parameters on the impact of MOR-CB_1 interaction on drugs and drug combinations effects at the cellular and molecular level (Cuna, 2025; Renault et al., submitted to Communication Biology).

These approaches help capture drug interactions at the molecular level, by integrating receptor dynamics into larger pharmacological and systems models. Their inclusion within the QSPainRelief 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 towards more precise, safer and effective multimodal analgesic strategies. The in vitro molecular pathway analysis, carried out in the frame of the structural modelling approach, provided valuable information and quantitative pharmacological parameters about how and to what extent receptor heteromerisation may impact on the downstream molecular effects elicited by morphine, THC, or a combination of the two. Considering that, depending on the extent of receptor heteromerisation, receptor activation by its agonist (e.g., morphine) can be either increased or significantly attenuated, the full inclusion of these parameters into the QSPainRelief platform that we aim to complete in the near future will help identify more effective and safer analgesic strategies (i.e., in case of additive/synergistic effects, drug doses could be tailored to minimise adverse effects whilst retaining relevant analgesia).

5.2.3 | 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 6 (Geerts et al., 2016). Drug-induced receptor activation changes can lead to ion-channel conductance variations via a transfer function. The model output then tracks changes in neuronal firing and network activity which are subsequently mapped to clinical endpoints such as pain intensity, cognitive performance, sedation scores and drug-liking measures (Figure 6). The platform is based on Hodgkin-Huxley-type neuron models, modulated by neurotransmitter systems with accurate anatomical and receptor localisation. It currently includes over 30 molecular targets across key CNS pathways. The models are humanised using data from PET, MRI, BOLD (blood oxygenation level dependent) imaging, genomic datasets and postmortem studies in both healthy and disease-specific populations. The QSPainRelief model platform is calibrated and validated by simulating the effects of drugs and doses from historical clinical trials and comparing the neurological outputs of the QSP neural circuit models, for example, average firing rate of projection neurons from the dorsal horn to reported outcomes such as average patient reported outcome of pain intensity (Step 4 of Figure 6). This was done for all four indications, as detailed in the next section.

Functional neural circuits for pain, sedation, cognition and abuse liability

In Step 3 of Figure 6, three neural network models representing circuits relevant to analgesia, cognitive impairment, sedation and abuse liability were used to simulate neuronal responses to drug exposure. To simulate pain relief, neural activity was modelled in the dorsal root ganglion and dorsal horn (Medlock et al., 2022). This network model was then extended to the rostral ventromedial medulla, periaqueductal grey, thalamus and primary somatosensory cortex where changes in pyramidal cell firing is linked to changes in pain intensity. For sedation and cognitive impairment, networks of neurons (circuits) covering the prefrontal cortex, striatum, globus pallidus externa/interna, subthalamic nucleus and thalamus have been modelled and their responses simulated (Roberts et al., 2012; Spiros et al., 2017). For cognitive effects, half of the pyramidal cells are stimulated, and their firing activity is linked to accuracy in a two-back working memory task (Geerts et al., 2013). For sedation effects, no stimulus is applied so

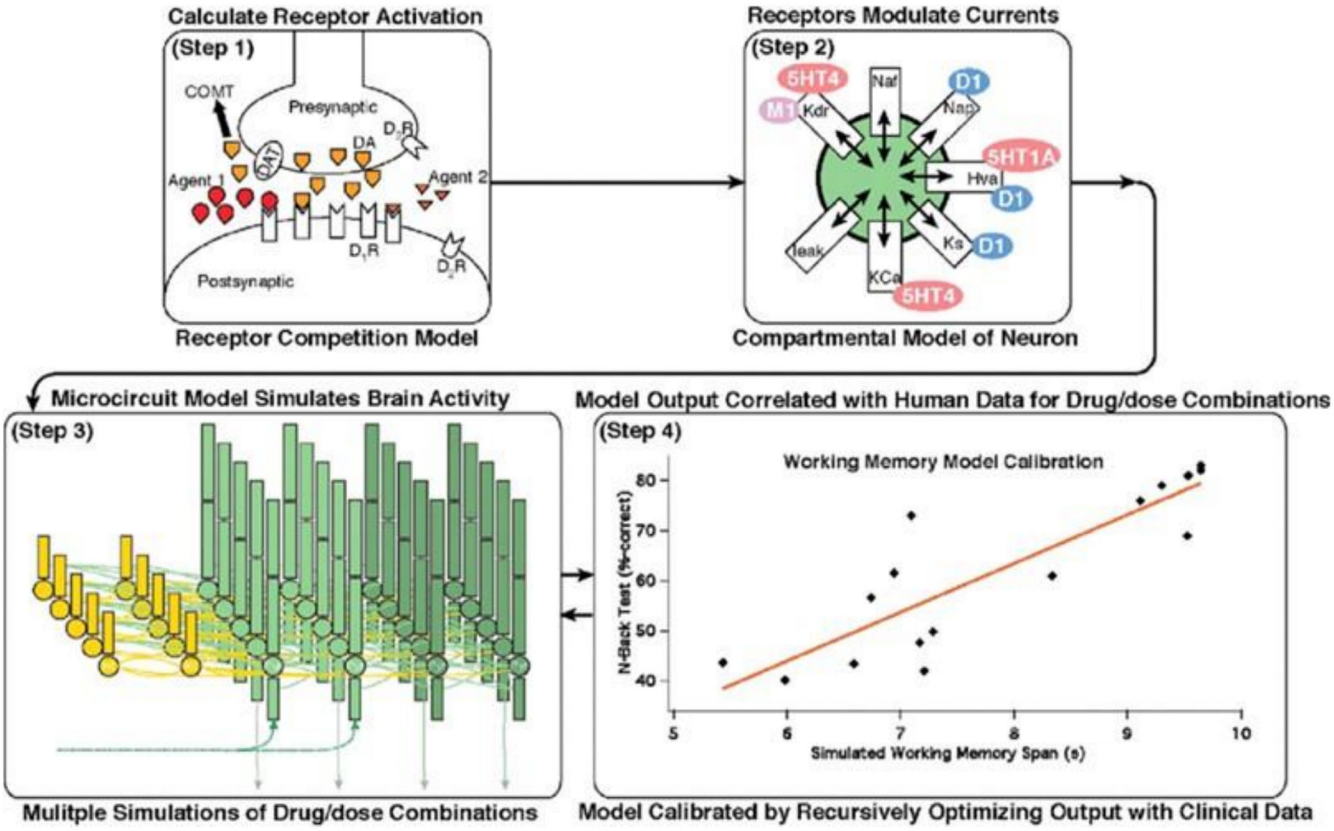

FIGURE 6 (Step 1) Determine target engagement of drugs. (Step 2) Incorporate effects of targets on neuronal mechanisms such as conductance on ion channels. (Step 3) Simulate drug effects on a system of neurons to determine resulting neuronal network behaviour. (Step 4) Simulate known drug clinical outcomes, modifying the effect size set in Step 2 to maximise the correlation (R^2) between model readout (*x*-axis) and clinical outcomes (*y*-axis).

that the network is in a resting state and the activity of the cortical neurons are aligned with reported somnolence levels from clinical data. To assess drug abuse liability, dopamine neurons and GABAergic interneurons were modelled in the ventral tegmental area, affecting ventral dopamine concentrations which are then linked to 'drug liking' scores (Kuznetsova et al., 2010; Spiros et al., 2010).

6 | QSPAINRELIEF MODEL PLATFORM CALIBRATION AND VALIDATION

6.1 | Calibration

Calibration involved adjusting model parameters to match observed outcomes from hundreds of published clinical trials on drugs for chronic pain (~250 trials in total). Specifically, calibrating the neuronal circuit models requires implementation of the drugs' mechanisms of action as shown in Figure 6. As an example, let us consider how the effects of morphine are brought into the model of analgesia. Morphine works at the mu-opioid receptor (MOR). MORs exist throughout the brain but, for this example, let us consider the effect on neurons in the DRG. MOR activation decreases high voltage-activated Ca-channel currents (Moy et al., 2020). As described in Geerts et al. (2016), instead of following the intracellular cascade, we bring in this effect with a change in the Ca-channel maximum conductance such that g_max_new = g_max_old * (1 − P * MOR_drug) where P is the parameter that is to be determined by calibration and MOR_drug is the normalised effect of the drug on the MOR. If the drug does not affect MOR, then MOR_drug = 0 and there is no change in the channel conductance. If the drug is a full agonist and its dose is such that it binds all MOR, then MOR_drug = 1 and the channel conductance is reduced by 1 − P, also showing the need for the restraint $P < 1$. For every drug and dose that affects MOR and for which we have results on its change in pain intensity from clinical results, we are able to simulate its outcome in our analgesic neuronal model by applying the MOR_drug value associated with that particular drug and dose through PK and BK modelling (Step 1 of Figure 6). This results in a graph of ordered pairs (the points in Step 4 of Figure 6) where the result of the simulation is plotted for the x-coordinate, and the corresponding clinical result is plotted for the y-coordinate. Changing the value of P ends up affecting the simulation outcomes, in essence sliding the points left and right. When we look at the regression line through these points, we were able to determine how well it fits them with its R^2 value. Thus, we have turned the problem of calibration to an optimisation problem where one is looking to adjust the value of P, restricted to biologically reasonable values, such that it maximises R^2. Furthermore, the linear relationship between the simulation output and the clinical outcome allows us to determine an estimate of the clinical response (in this case the change in pain intensity) for any drug or drug combination based on its simulation result.

In the example above, we have simplified the problem to just one parameter P that is affected by MOR agonism. However, we know that MOR are located throughout our analgesia model. Thus, we have similar mechanisms in place affecting many more neurons in different brain regions. Thus, we have a set of P_i that need to be adjusted simultaneously to maximise R^2 with the further constraint that P_i on similar mechanisms should be the same.

For receptors that are affected by neurotransmitters such as dopamine, **norepinephrine** and serotonin, determining the effect of drugs on these receptors is accomplished by considering the average 'activation' of these receptors when the drug and neurotransmitter are in competition so that the activation takes the place of MOR_drug (Spiros et al., 2010). This allow us to include many mechanisms of drugs in the models which all need to be calibrated based on the relationship between the simulated neuronal responses and their clinical results for all four indications. Thus, the clinical data gathered to calibrate and validate the models is very large.

6.2 | Validation

Validation is a prerequisite for acceptance of any modelling platform in a clinical setting. The QSPainRelief platform was validated by comparing its predictions for individual and combination therapies with independently published trial results not used during the calibration procedure. Additional validation came from evoked pain studies in healthy subjects and clinical trials in patients with chronic pain, where predicted analgesic and side-effect profiles compare well with observed outcomes. Additional validation is provided by preclinical PK-PD studies that were conducted in rodent models of neuropathic pain (Bura et al., 2013; Bura et al., 2018; Cabañero et al., 2020) and PK-PD evoked pain studies that were conducted in healthy participants—assessing morphine, pregabalin and **fluvoxamine** combinations (Bakker et al., 2025), complemented by data from ongoing clinical studies in patients with chronic pain initiating a treatment prescribed by their treating physician (NCT04742790). These studies, conducted for the purpose of validation, included a set of predefined and aligned PD markers sensitive to drug effects on nociceptive processing, vigilance and cognitive function (Bakker et al., 2025; Gosset et al., 2025), as well as patient-reported outcomes related to analgesia and side effects, as detailed in Table 2. In addition, a novel operant animal model was employed to evaluate spontaneous pain relief, together with operant measures of cognition and sedation (Cabañero et al., 2022). This approach allowed for a more integrated and translational outcome, comparable to human data.

Validation of the individual model components underlying QSPainRelief predictions—including drug exposure, target engagement, pharmacodynamic neural responses and clinical outcomes—is performed at multiple levels using preclinical, healthy volunteer and patient datasets. Because this validation spans multiple model components and is still ongoing, a comprehensive quantitative assessment is beyond the scope of the present publication, which aims to describe the conceptual framework and translational potential of the approach. We therefore provide instead an illustrative example of

TABLE 2 PK-PD evoked pain studies in healthy participants—assessing morphine, pregabalin and fluvoxamine combinations, complemented by data from ongoing clinical studies in patients with chronic pain initiating a treatment prescribed by their treating physician (NCT04742790). These studies, conducted for the purpose of validation, included a set of predefined and aligned PD markers sensitive to nociceptive processing, vigilance and cognitive function, as well patient-reported outcomes related to analgesia and side effects.

	Published clinical trials	Preclinical studies	Healthy-volunteer PK/PD studies	Clinical studies in patients
Nociceptive processing/ analgesia	Pain intensity (VAS/NRS) or related PROs	Thermal hyperalgesia (plantar test) and mechanical allodynia (von Frey) in sham and in a model of neuropathic pain (partial sciatic nerve ligation)	Heat pain threshold, cold pressor test, tourniquet pain, electrical pain, conditioned pain modulation, thermal grill illusion, thermal pain after topical capsaicin and after UVB radiation	Contact heat-evoked potentials and heat pain ratings, pinprick sensitivity, N13 cervical component of upper-limb somatosensory evoked potentials (as an index of dorsal horn function), short form brief pain inventory (SF-BPI), VAS pain intensity
Sedation. sensorimotor coordination	Sleepiness scales	Locomotor activity and motor coordination (rotarod test)	Saccadic eye movements, resting EEG (eyes open and eyes closed), Stanford sleepiness scale, adaptive tracking task, body sway test, pain and sleep questionnaire (PSQ3)	Saccadic eye movements, resting EEG (eyes open and eyes closed), Stanford sleepiness scale, adaptive tracking task, body sway test, group somnolence level
Memory	N-back working memory test	Novel object recognition test	N-back working memory test, visual verbal learning test	N-back working memory test
Cognition		Self-medication cognitive performance	VAS cognition	Cognitive P300 evoked potentials, PROMIS Neuro-QOL SF cognitive function
Mood		Elevated T maze test, tail suspension test	VAS Bond & Lader	SF BPI (mood)
Drug abuse liability	Drug abuse liability test	VAS Bowdle (psychedelic effects)		VAS drug liking

how the platform can generate model-based predictions for drug combinations.

6.3 | Predicting the effects of drug combinations

Because co-medications with morphine show negligible impact on CNS drug concentrations (Gülave, Lesmana, et al., 2025), drug combinations with morphine were simulated by independently combining their target effects according to the BK and neural circuit models. Because we are dealing with chronic pain and are interested in longer term drug use as well as plasticity changes due to long-term opioid use, we used the average daily brain ECF and CSF–SAS drug concentrations after 4 weeks except in the case of drug abuse liability where the maximum brain ECF drug concentrations within the first 24 h were used. Using these regional CNS drug concentrations, we were then able to determine the effects of each co-medication at its independent non-opioid receptor target when combined with morphine and simulate the combination as the effects were applied to the neural circuit models. For dose-sparing analyses, we modelled five morphine dosing regimens (0, 15, 30, 45 and 60 $mg \cdot day^{-1}$) combined with three regimens of over 30 augmentation drugs, across the four indications. This resulted in simulations of 450+ combinations.

A key illustrative result is derived from the combination of morphine 30 $mg \cdot day^{-1}$ (10 mg dose taken three times per day) with **duloxetine** 40 $mg \cdot day^{-1}$ (taken once per day). The LeiCNSPK3.0 model provides average brain ECF concentrations after 4 weeks. The concentration of morphine acts as input for the LeiCNSBK1.0 model to estimate morphine's binding to MOR. The concentration of duloxetine acts as input to the cleft simulations where it inhibits serotonin and norepinephrine reuptake, leading to increased synaptic levels of both neurotransmitters. These changes in neurotransmitter availability modify serotonin and norepinephrine receptor activation which are input into the circuitry models along with MOR activation. These receptor activations alter the conductance of specific ion channels across all four indications within the circuitry models. The resulting modifications in neuronal firing are read out and linked to clinical outcomes according to the aforementioned calibration, resulting in a score of 3.4 points improvement in VAS pain intensity for analgesia, 0% somnolence for sedation, 70.5% correct in a two-back working memory test for cognition, and a drug liking VAS of 60.8 (on a scale of 0–100 with 50 being neutral) for abuse liability.

6.4 | 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 CUI which is a benefit–risk assessment tool. These tools weigh the benefits (e.g., desired treatment effect) against the risks (e.g., side effects). They can be classified under a qualitative or quantitative framework.

Benefit–risk assessment tools 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. 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 (Figure 7) (U.S. Food and Drug Administration, 2023).

For CUI, a quantitative framework, 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, normalisation or cut-off) (Winzenborg et al., 2021). 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.

Major advantages of a CUI model include its transparency and consistency, as well as the ability to interpolate/extrapolate across doses. It also allows applying alternative weights based on clinician input, patient preference or patient stratification (e.g., sex and age). In addition, CUI models can be easily integrated with model-predicted outcomes from PKPD and QSP models. Within the QSPainRelief platform, we implemented this approach by linking the QSPainRelief models predicting analgesic responses and side effects of combination treatments for chronic pain into a CUI model to predict which drug combinations are most likely to provide optimal benefit for patients.

Furthermore, we developed a proof-of-concept application in which CUI weights are derived from clinician inputs: 1, 0.5, 0.2 and 0.1 for pain, sedation, cognitive impairment and drug abuse liability, respectively. These are applied to the normalised outputs for each indication such that the minimum outcome receives a value of 0 and the maximum outcome receives a value of 100. For example, the simulated combination of morphine and duloxetine (above) produced a calculated CUI score of 32.49, which was higher than that of either drug alone. The result is preliminary and expected to change with model improvements and patient dictated weights.

In line with regulatory recommendations, patient preferences are subsequently being incorporated. To capture these preferences, we designed an online questionnaire for patients with chronic pain, collecting data on treatment preferences across different stratifications such as pain type and severity, current side effect burden, sex and ethnicity. Data gathering has started. This data will inform the CUI model, allowing patient characteristics to be explicitly considered, which eventually could lead to better personalised pain treatments. The resulting patient-derived weights will be integrated alongside those provided by clinicians.

As one of the publicly available deliverables, the results of a CUI model (app_v2025_07v5) are provided. It was informed by the QSPainRelief model platform predictions of endpoints representing analgesia, sedation, cognitive impairment and drug abuse liability, for compounds in combination with morphine, to see what drug combination would benefit chronic pain patients. Using clinician informed weights of 1 for analgesia, 0.5 for sedation, 0.2 for cognitive impairment and 0.1 for drug abuse liability; the compound in combination with morphine that is predicted to benefit the patient the most is **nortriptyline**. So, this is the number one ranked combination compound. Other top contenders that are predicted to do well are (unordered): **aripiprazole**, **atomoxetine**, **desvenlafaxine** and duloxetine from deliverable D4.4 Page 4 H2020 research and innovation programme QSPainRelief. It also shows that when grouping each drug according to the Anatomical Therapeutic Chemical (ATC) classification, we can rank the drug classes that perform best* with lower doses of morphine as a comedication based on their average CUI scores:

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

FIGURE 7 FDA's benefit–risk Framework for New Drug Review. U.S. Food and Drug Administration.

	Ranking by drug class (top 4)	CUI score	Compounds within the class
1	Serotonin–norepinephrine reuptake inhibitors (SNRIs)	32.49	Desvenlafaxine, duloxetine, **milnacipran**, **venlafaxine**
2	Norepinephrine reuptake inhibitor (NRI)	30.24	atomoxetine, **reboxetine**
3	Selective serotonin reuptake inhibitors (SSRI)	29.91	**Citalopram**, **escitalopram**, **fluoxetine**, fluvoxamine, **paroxetine**, **sertraline**
4	Tricyclic antidepressants (TCAs)	25.92	**amitriptyline**, **clomipramine**, **desipramine**, **doxepin**, **imipramine**, nortriptyline

** Disclaimers: First of all, this is not medical advice. Second, the model scores are derived from three predicted side effects. These do not encompass all the side effects that come with analgesics such as nausea, constipation, dry mouth, unintentional weight gain and even death due to respiratory arrest. Third, the modelled pathways do not cover all mechanisms involved in analgesia; this also reflects in the selection of the compounds which is among others based on mode of action being present in the model.* (https://qspainrelief.eu/wp-content/uploads/2025/08/Deliverable-report_D4.4_Final.pdf).

7 | FUTURE DIRECTIONS FOR THE USE OF THE QSPAINRELIEF MODEL PLATFORM

Several opportunities exist to further enhance the utility of the QSPainRelief model platform, which are outlined below.

7.1 | Molecular drivers

One of the more fundamental drivers is the limited understanding of the complex and dynamic physiological processes that contribute to the chronicity of pain. Mechanisms such as peripheral and central sensitisation, altered descending inhibition or facilitation or ectopic neuronal discharges remain only partially characterised, particularly in human subjects. This knowledge gap limits the ability to fully represent pathological states within the current QSPainRelief model platform.

7.2 | Preclinical animal models for pain

Another direction where further focused studies are needed are the challenges in translation between animal models for pain, and human pain conditions. Whereas the QSPainRelief model platform provides a structured framework to integrate human data, further steps towards translation of preclinical studies are complex. The current mice model is multidimensional in terms of PD outcomes that may reflect a substantial spectrum of neuropathic pain with multidimensional PD outcomes on analgesia and side effects as sedation, cognitive impairments and abuse liability of antipain drugs and combinations thereof. To this end, repeated non-contingent drug administrations, together with PK analysis of drugs (and combinations thereof) in neuropathic pain animal models (Bura et al., 2013; Bura et al., 2018; Cabañero et al., 2020), were used to better mimic the observed phenotypes. Non-contingent administration is more controllable and replicable, whereas contingent (operant) administration represents a more translational model. Thanks to this combined approach, the platform can be supplied with complementary results, allowing refinement of the predictions based on the study design. However, the mice models on neuropathic pain cannot cover all chronic pain phenotypes. Moreover, the current mice model is based on a dose–response approach. Also, there is a need for including assessment of (unbound) plasma and CNS PK profiles, to be related to the PD outcomes. As a result, current neural circuit models embedded in the QSPainRelief model platform require further refinement to simulate clinically relevant pathophysiological states.

7.3 | Condition-specific mechanisms

Future developments in QSPainRelief will require the incorporation of condition-specific mechanisms contributing to chronic pain into the existing neural network models. In its current state, the QSPainRelief model platform does not explicitly model disease-related alterations in PK processes, nor nociceptive processing that are thought to underlie chronic pain states, including the mechanisms contributing to nociceptive/inflammatory, neuropathic and nociplastic pain (De Lange, 2013a). Extending the CNS PBPK, CNS BK and neural circuit models to specific chronic pain conditions can be achieved by adjusting model parameters to reflect mechanism-specific changes in function, such as changes in plasma protein binding, BBB transport, receptor expressions, endogenous ligand concentrations, maladaptive neuroplasticity, chronic inflammation or neuropathic-like features including spontaneous neuronal firing or loss of inhibitory tone. Integration of omics data, patient stratification biomarkers and longitudinal clinical outcomes could further enhance the model's predictive value and personalisation capacity (De Lange et al., 2017).

Ultimately, advancing QSPainRelief model platform for analgesic drug development and treatment modalities will depend on deeper pharmacokinetic, target engagement and disease related biological insights into pain chronification and more robust, human-relevant datasets to support model calibration and validation. How to proceed?

7.4 | Emerging treatments

Beyond optimising existing analgesic drug combinations, future applications of QSP may extend to emerging treatments with novel mechanisms of action, such as **$Na_V1.8$**-selective modulators, and in the longer term, non-small molecule approaches. Whereas these

strategies pose additional challenges in terms of mechanistic representation, the multiscale structure developed within QSPainRelief provides a conceptual foundation for in silico modelling of the effects of such therapies, including their potential. In a broader perspective, similar modelling concepts could be explored for non-pharmacological interventions, such as neuromodulation, within multimodal pain management strategies.

7.5 | Integrative data

The QSPainRelief model platform needs to be (further) developed, informed by high quality data (i.e., smart data). Parameter values of PK, PD and disease processes should not be obtained in isolation, and in different systems, because in such manner inter-relationships and systems dependencies of processes cannot be assessed (De Lange, 2013a). In the QSPainRelief platform we have made important first steps in this direction by creating a comprehensive database which connected in vitro, in vivo and clinical data in a FAIR manner, facilitating QSP model-based approaches.

8 | CONCLUSIONS

Chronic pain represents a major clinical and societal burden and often proves resistant to pharmacological treatments. Combination therapies are increasingly explored as a strategy to enhance efficacy, minimise side effects and reduce reliance on high-dose monotherapies. In this context, QSP is a powerful framework to identify optimal treatment strategies by mechanistically linking 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 CNS PBPK modelling, target binding kinetic models and neural circuit model simulations. The QSPainRelief platform provides a mechanistic framework that may support rational drug pairing, optimisation of dose regimens and a significant reduction in the reliance on trial-and-error strategies in both preclinical and clinical settings. Furthermore, QSPainRelief provides a mechanistic framework that could be used to incorporate individual variability such as variability due to age, sex, receptor expression and comorbidities and thereby evolve into a tool for more personalised combination treatment strategies.

Key takeaways from this work include the demonstration that integrating PK and PD across biological scales enables mechanistically informed estimation of CNS target engagement and associated clinical outcomes. Importantly, the QSPainRelief platform can evolve to allow pathophysiological mechanisms relevant to chronic pain to be represented as tuneable model states, enabling the simulation of distinct mechanistic pain profiles, and their modulation by pharmacological interventions. The QSPainRelief model platform also provides a means to design opioid-sparing combinations, thereby addressing both efficacy and safety challenges in chronic pain therapy. In addition, the use of CUI represents a novel and important component of the QSPainRelief framework, providing a structured patient-centred benefit–risk evaluation that directly links model predictions to clinically meaningful decision making.

Future research will focus on expanding the QSPainRelief model 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, the QSPainRelief model platform represents a key enabler for more effective, safer and personalised chronic pain management.

8.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in https://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander, Davenport, et al., 2025; Alexander, Gibb, et al., 2025).

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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