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Towards personalized treatment of pain using a quantitative systems pharmacology approach

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ABSTRACT

Pain is a complex biopsychosocial phenomenon of which the intensity, location and duration depends on various underlying components. Treatment of pain is associated with considerable inter-individual variability, and as such, requires a personalized approach. However, a priori prediction of optimal analgesic treatment for individual patients is still challenging. Another challenge is the assessment and treatment of pain in patients unable to self-report pain. In this mini-review, we first provide a brief overview of the various components underlying pain, and their associated biomarkers. These include clinical, psychosocial, neurophysiological, and biochemical components. We then discuss the use of empirical and mechanism-based pharmacokinetic-pharmacodynamic modelling to support personalized treatment of pain. Finally, we propose how these concepts can be extended to a quantitative systems pharmacology (QSP) approach that integrates the components of clinical pain and treatment response. This integrative approach can support predictions of optimal pharmacotherapy of pain, compared with approaches that focus on single components of pain. Moreover, combination of QSP modelling with state-of-the-art metabolomics approaches may offer unique possibilities to identify novel pain biomarkers. Such biomarkers could support both the personalized treatment of pain and translational drug development of novel analgesic agents. In conclusion, a QSP approach will likely improve our ability to predict pain and treatment response, paving the way for personalized treatment of pain.

1. Introduction

Pain has been defined as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage" (Merskey and Bogduk, 1994), and involves a complex interplay of neurophysiology (Vardeh et al., 2016), psychosocial factors (Mao, 2012), and inflammatory processes (Ji et al., 2016). Pain and treatment response for both acute and chronic pain is associated with substantial inter-individual variability (Aubrun et al., 2012; Gilron et al., 2013; Hinrichs-Rocker et al., 2009). For acute postoperative pain, analgesic drugs are generally titrated based on the patient's self-reported pain levels, because a priori prediction of effective pain treatment is difficult (Aubrun et al., 2012). In many chronic pain conditions, many patients do not achieve even moderate pain relief from the various available drug therapies (Gilron et al., 2013). Consequently, for chronic pain there is a need to predict both the type of drugs and their dosage regimen that will optimally treat the individual patient. Finally, not all patients are able to self-report pain, for instance due to unconsciousness, cognitive impairment or young age (< 3 years).

There is a major unmet clinical need for biomarkers and patient characteristics that can guide personalized treatment of pain in the individual patient. Various components underlie the large inter-individual variability of pain and treatment response, including clinical, psychosocial, neurophysiological and pharmacological components (Apfelbaum et al., 2003; Borsook et al., 2011; Hinrichs-Rocker et al., 2009). By providing a quantitative insight into the underlying compo-

Abbreviations: COX-2, cyclooxygenase-2; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; NSAIDS, non-steroidal anti-inflammatory drugs; PET, positron emission tomography; PD, pharmacodynamics; PK, pharmacokinetics; QSP, quantitative systems pharmacology

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nents of pain, biomarkers for pain or treatment response could contribute to personalized treatment in several ways: i) pain monitoring in patients where self-report is not possible ii) diagnosis of pain conditions iii) a priori prediction of optimal treatment (Backryd, 2015; Beger et al., 2016). Additionally, biomarkers of treatment response can contribute to dose-finding during drug development (Frank and Hargreaves, 2003; Taneja et al., 2016).

Characterizing the inter-individual variability in the underlying components of pain might support the personalized treatment of pain. For example, patient-specific predictors of pharmacokinetics have been used to optimize morphine dose regimens in pediatric patients (Krekels et al., 2014). However, the right drug and dose regimen for individual patients are unlikely to be predicted on the basis of pharmacokinetics alone (Krekels et al., 2014). Arguably, the lack of studies integrating the aforementioned components underlying pain and treatment response is prohibiting development of personalized medicine strategies. In our view, pain cannot be truly understood mechanistically nor well predicted, when components of the underlying system are studied in isolation. Thus, an approach that integrates these components would support the use and development of biomarkers to guide personalized treatment of pain.

In this report, we first provide an overview of outcome metrics and candidate biomarkers of pain, and the pain-related (biological) processes that they inform on (Table 1). Next, we discuss the use of empirical and mechanism-based pharmacokinetic-pharmacodynamic modelling of clinical pain. Finally, we propose how these concepts can be extended to a quantitative systems pharmacology (QSP) approach that integrates the components and biomarkers of clinical pain to enable personalized treatment.

2. Underlying Components of Clinical Pain

2.1. Clinical Pain Assessment

Patient self-reporting is the gold standard for clinical pain assessment (Herr et al., 2011; McCaffery, 1968). Typically, unidimensional scales are used, such as the visual analogue scale and numerical rating scale (Younger et al., 2009). Multidimensional pain scales have additional items that incorporate other aspects of pain, such as impact on quality of life and interference with daily life. Such factors are especially relevant in chronic pain conditions, where pain intensity ratings alone correlate poorly with the impact on quality of life (Lame et al., 2005). Examples of multidimensional pain scales include the West Haven-Yale Multidimensional Pain Inventory and the Treatment Outcomes of Pain Survey (Kerns et al., 1985; Rogers et al., 2000).

Behavioural pain scales are used to assess pain in patients unable to self-report (Herr et al., 2011). Examples of such scales include the COMFORT behaviour scale for neonates and infants, and the REPOS and PAINAD scales for patients with advanced dementia (van Dijk et al., 2000; van Herk et al., 2009; Warden et al., 2003). Such scales quantify pain-associated behaviour, such as facial tension, moaning and crying. It is, however, difficult to discriminate between behaviour from pain and that from other sources of emotional or physiological distress (Herr et al., 2011; Pasero and McCaffery, 2005). Alternative surrogate pain markers focusing on autonomous nervous system responses include skin conductance, heart rate variability and pupillometry (Cowen et al., 2015). However, similar to the behaviour scales, these markers are affected by both pain and other types of distress (Baarslag et al., 2017).

2.2. Psychosocial Contributors to Clinical Pain

Pain perception and treatment response are influenced by a number of psychosocial factors including psychiatric comorbidities (e.g., depression, anxiety, stress), social support, and patient expectations (e.g., nocebo and placebo effects) (Colloca et al., 2013; Gil et al., 1990; Hinrichs-Rocker et al., 2009; Ip et al., 2009; Linton and Shaw, 2011; Masselin-Dubois et al., 2013; Sturgeon and Zautra, 2013; Wiech, 2016). One example is pain catastrophizing, which is the tendency to feel helpless about pain, to magnify the perceived threat level of pain and to be unable to inhibit pain-related thoughts (Quartana et al., 2009; Sullivan et al., 1995). Pain catastrophizing has been associated with a decreased response to analgesic treatment and worse pain-related outcomes (Fillingim et al., 2005; Haythornthwaite et al., 2003; Quartana et al., 2009).

Placebo and nocebo effects can respectively induce relief or increased pain experience through expectation and previous experience (Reicherts et al., 2016). Additionally, placebo analgesia has a strong neurobiological component, with involvement of various endogenous neuromodulators (Colloca et al., 2013). The effect of placebo can be quantified separately from the drug effect in studies that include placebo treatment arms (Anderson et al., 2001; Bjornsson and Simonsson, 2011). However, when effective treatment exists, treatment with placebo alone might not be ethically possible, thus limiting the ability to quantify the placebo effect (Arnstein et al., 2011). Another approach to study the contribution of placebo analgesia is the comparison of covert and overt administration of analgesics. For example, Amanzio et al. showed that required doses are higher if analgesics are administered covertly, indicating the contribution of placebo effects to the clinical efficacy of analgesics (Amanzio et al., 2001).

2.3. Neurophysiological Biomarkers

The neurophysiology of pain has been extensively studied with electrophysiological and imaging techniques (Lee and Tracey, 2013; Schweinhardt and Bushnell, 2010). Brain imaging studies have linked activity in several regions of the brain to pain and nociception, however, none of these areas are exclusively activated by pain nor do any of these appear to be crucial for pain experience (Melzack, 2001). Additionally, these techniques can be used to identify differences in the neurophysiology of pain in special patient populations (e.g., children of various age groups) (Sava et al., 2009).

Thus far, it has proved challenging to use neurophysiological biomarkers to quantify pain levels in the individual patient with sufficient sensitivity and specificity (Davis et al., 2012). However, on a population level, several neurophysiological biomarkers have been associated with pain. For example, an EEG-based template was recently proposed as a measure for nociceptive brain activity in infants (Hartley et al., 2017). A priori predictors from fMRI have emerged in areas of experimental pain, postoperative pain, and chronic pain (Baliki et al., 2012;Gram et al., 2017; Huang et al., 2013; Lee and Tracey, 2013). For example, brain activity in regions associated with emotional appraisal during anticipation of pain can partially predict inter-individual variability in placebo response (Colloca et al., 2013). Additionally, imaging might contribute to clinical differentiation of chronic pain subtypes (Borsook and Becerra, 2011).

Imaging approaches form a potential method to characterize the neurophysiological interactions between pain, nociception, psychology and analgesic treatment. For example, PET and fMRI studies have linked placebo analgesia to opioidergic pathways of descending pain modulation in the anterior cingulate cortex, the periaqueductal grey and the spinal dorsal horn (Lee et al., 2014). It has also been suggested that placebo and nocebo effects act on distinct areas of the brain (Bingel et al., 2011; Lee et al., 2014). Pain catastrophizing has been associated with altered pathways of endogenous pain inhibition, and increased activity in regions associated with the anticipation, attentional and emotional aspects of pain (Quartana et al., 2009). Finally, the treatment of pain with opioids and NSAIDs has been linked to changes in the activity of pain-related regions, and some studies have even looked at the sensitivity of different regions to these pharmacological effects (Hodkinson et al., 2015; Lee et al., 2014; Oertel et al., 2008).

Table 1
Overview of candidate biomarkers and outcome metrics of clinical pain.

Candidate biomarkers and outcome metrics	Examples	Associated processes	Advantage(s)	Limitations	Evidence level[a]	Role in QSP of pain[b]	Modelling methods[c]	Suggested references
Self-report pain: Unidimensional scales	VAS, NRS, VRS	Pain perception	Gold standard of pain assessment	Patient not always capable of self-report	+ +	Dynamic outcome measure	Continuous or categorical PKPD	(Younger et al., 2009)
Self-report pain: Multidimensional scales	WHYMPI, TOPS, SF-MPQ	Pain perception, quality of life	Provides more information than unidimensional scales	Patient not always capable of self-report	+ +	Dynamic outcome measure	Continuous or categorical PKPD	(Younger et al., 2009)
Behavioural pain scales	COMFORT scale for neonates and infants; REPOS and PAINAD for patients with advanced dementia	Pain-associated behaviour	Provides a method of pain assessment when self-report is unavailable	Does not directly quantify pain perception Discrimination between pain and other sources of distress difficult	+	Dynamic outcome measure	Continuous or categorical PKPD	(Herr et al., 2011)
Autonomous nervous system responses	Skin conductance, pupillometry, heart rate variability,	Autonomous nervous system activation	Performed at bedside	Discrimination between pain and other sources of distress difficult	+/−	Dynamic biomarker or covariate	Continuous or categorical PKPD	(Cowen et al., 2015)
Psychosocial assessments and questionnaires	Depression, chronic stress, anxiety, fear, pain catastrophizing scale, spousal support	Psychological comorbidities, expectations, social support	Non-invasive, potential predictor of pain	Certain assessments require trained personnel	+/−	Dynamic biomarker or covariate	Continuous or categorical PKPD	(Sturgeon and Zautra, 2013) (Colloca et al., 2013) (Wiech, 2016)
Neurophysiology	MEG, EEG, NIRS	Pain-associated brain activity	Performed at bed-side	Poor spatial resolution Limited specificity/ sensitivity for pain	+/−	Dynamic biomarker or covariate	Continuous PKPD, multivariate statistics/ machine learning, structural equation modelling, dynamic causal modelling	(Lee and Tracey, 2013) (Pinheiro et al., 2016)
Central nervous system MRI	Functional MRI, resting-state MRI, magnetic resonance spectroscopy	CNS activity, CNS connectivity, brain structure, brain chemistry	High spatial resolution	Costs Bedside use not possible Limited specificity/ sensitivity for pain	+/−	Dynamic biomarker or covariate	Continuous PKPD, multivariate statistics/ machine learning, structural equation modelling, dynamic causal modelling	(Borsook and Becerra, 2011; Davis et al., 2012) (Lee and Tracey, 2013)
Molecular profiling: genomics	Polymorphism in metabolising enzymes, drug transporters, μ-opioid receptor, cytokines	Pharmacokinetics, nociception, endogenous pain modulation, inflammation	Decreasing costs make routine genotyping increasingly more feasible	Does not take environmental influences into account, thereby only explaining part of the variability.	+/−	Static covariate	Categorical covariate	(Mogil, 2012)
Molecular profiling: metabolomics/ proteomics	Inflammatory markers, endocannabinoids, endogenous opioids, stress hormones	Inflammation, endogenous pain modulation, stress response	Closer to the clinical phenotype than genomics.	Subject to confounding environmental factors. Sampling at the site of action might not be feasible; profiles in blood might not be representative.	+/−	Dynamic biomarker or covariate	Multivariate statistics/ machine learning, network analysis, mechanistic PKPD	(Backryd, 2015)
Drug exposure	Drug concentration (predicted or measured with therapeutic drug monitoring)	Pharmacokinetics	Model-based predictions of drug exposure can guide pharmacotherapy	Variability in pharmacokinetics is only a part of the variability related to pain and its treatment	+	Characterizes drug exposure in plasma or target site over time	Population pharmacokinetics	(Martini et al., 2011; Mould and Lesko, 2014)

Abbreviations: CNS, central nervous system; EEG, electroencephalography; MEG, magnetoencephalography; MRI, magnetic resonance imaging; NIRS, Near-infrared spectroscopy; NRS, numerical rating scale; PKPD, pharmacokinetics-pharmacodynamics; SF-MPQ; TOPS, Treatment Outcomes of Pain Survey; VAS, visual analogue scale; VRS, verbal rating scale; WHYMPI, West Haven-Yale Multidimensional Pain Inventory.

[a] Level of evidence notation: + +, direct self-report of pain (gold standard); +, generally accepted proxy measure or predictor of pain or treatment response, (suitable for) routine clinical use; +/− promising, but additional evidence is required for routine clinical use.

[b] The word 'covariate' is meant to indicate an 'a priori predictor of (other) biomarkers or outcome', generally by explaining part of the variability on one of the model parameters.

[c] Examples of modelling methods for categorical data include proportional odds, Markov models and item response theory models.

2.4. Molecular Profiling of Pain

Molecular profiling technologies (e.g. genomics, transcriptomics, proteomics, metabolomics) provide quantitative insight into the biological processes that underlie clinical pain (Chen and Snyder, 2013; Wishart, 2016). Examples of these processes include inflammation, endogenous pain modulation, and nociception (Backryd, 2015; Chizh et al., 2008). While blood may not the primary matrix of interest for pain and nociception, biomarker profiles in blood related to signalling molecules might still capture these pain-associated biological processes in other tissues (Chen and Snyder, 2013). A large number of studies have implicated a role for genetics in the inter-individual variability in both experimental and clinical pain (Mogil, 2012). However, genetic associations have so far not been consistently replicated, nor have robust genetic predictors of inter-individual variability been identified—with the exception of some hereditary monogenic pain disorders (Mogil, 2012).

Metabolomics aims to characterize the metabolome, i.e. the entire spectrum of small molecule products that result from genetic, transcriptional and environmental influences. Metabolomics provides the closest biochemical representation of an individual's clinical phenotype and is therefore a promising source of new clinical biomarkers (Beger et al., 2016;Kohler et al., 2017 *this issue*). Proteomics can complement metabolomics as a source of candidate biomarkers, by quantifying proteins and peptides that function as signalling molecules in processes related to pain (Backryd, 2015). Currently, no single robust biomarker for pain perception has emerged from proteomic- or metabolomics approaches (Backryd, 2015). So far, potential pain biomarkers have been identified in processes such as inflammation (prostaglandins, cytokines, chemokines) and endogenous pain modulation (neuropeptides, endocannabinoids, neurosteroids) (Backryd et al., 2014; Kilts et al., 2010; Symons et al., 2015; Taneja et al., 2016). Additionally, metabolomics might also inform on psychological risk factors for increased pain, such as chronic stress and pain catastrophizing (Hinrichs-Rocker et al., 2009; Russell et al., 2012). For example, elevated salivary cortisol levels were predictive of pain catastrophizing in an experimental pain study that included pain-free subjects and subjects with chronic pain (Quartana et al., 2010). Finally, findings from metabolomics and proteomics studies have led to the discovery of candidate biomarkers of the underlying pathophysiology in several chronic pain conditions. In rheumatoid arthritis, biomarkers that reflect disease activity (e.g., auto-antibodies, collagen degradation products) might be predictive of clinical progression (McArdle et al., 2015). As such, they might inform which patients would benefit most from aggressive treatment. In inflammatory bowel disease (IBD), biomarkers in serum and faecal matter aid clinical diagnosis (i.e., differentiating IBD from non-inflammatory disorders) and have a potential for use in disease prognosis (Iskandar and Ciorba, 2012).

3. From Empirical to Mechanism-based Pharmacokinetic-pharmacodynamic Modelling of Pain

Pharmacokinetic-pharmacodynamic (PK-PD) modelling aims to quantitatively characterize the dynamic exposure-response relationships of drugs. Here, the response can reflect any marker associated with drug efficacy or toxicity (Breimer and Danhof, 1997). PK-PD modelling has become an increasingly important tool in both drug development and personalized medicine (Mould and Upton, 2012). Typically, PK-PD models are used in association with a nonlinear mixed effect modelling framework, which allows quantification of inter-individual variability. Predictors for such variability (including metabolomic biomarkers) can be quantitatively incorporated in these models.

Population PK modelling is a widely accepted approach to derive personalized dosing regimens of analgesics by identifying patient-specific predictors for inter-individual variability in PK (e.g. age, body weight or organ function) (Komatsu et al., 2012; Krekels et al., 2014). PK-PD models for clinical pain typically characterize the empirical relationships between drug exposure and clinical pain scores (Anderson et al., 2001; Juul et al., 2016; Mazoit et al., 2007). These empirical PK-PD models contribute to quantitative understanding of analgesic exposure-response relationships, by estimating parameters like the maximum analgesic effect, the concentration of half-maximum effect and the effect-site equilibration rate constant (Martini et al., 2011). These models may also include predictors of the inter-individual variability of these parameters, which might be relevant for personalized treatment. For example, Byon et al. used PK-PD modelling in patients with fibromyalgia to quantify the effect of sex and age on the maximum analgesic effect of pregabalin (Byon et al., 2010).

Most PK-PD models lack a mechanistic basis or causal relationships between the different factors contributing to pain perception. Such empirical PK-PD models have therefore limited use for translational purposes, i.e. to make predictions between species or patient populations (Danhof et al., 2007). In some PK-PD studies however, biomarkers are used as a mechanistic link between drug exposure and clinical response. For example, Danhof and colleagues incorporated pro-inflammatory mediators as biomarkers for the pharmacological effect of COX-2 inhibitors and linked these to clinical responses in chronic inflammatory pain conditions (Huntjens et al., 2005; Taneja et al., 2016). Quantitative EEG has been used as a biomarker for mu-opioid receptor activity in both preclinical and clinical PK-PD modelling of opioids (Danhof et al., 2007). Because such mechanism-based PK-PD models characterize processes on the causal path between drug administration and effect, they have important advantages in terms of translation and prediction (Danhof et al., 2005).

4. Towards a Quantitative Systems Pharmacology Approach to Clinical Pain

Previous sections outlined the different components that underlie clinical pain and the diverse range of biomarkers and predictors associated with these components. However, the accurate prediction of optimal pharmacotherapy in individual patients remains a challenge. Arguably, this may be due to studies that focus on specific components and association biomarkers in isolation. Secondly, little is known about how the different system components and their biomarkers interact. For example, should we treat patients with psychological risk factors of postoperative pain with higher analgesic doses?

Clinical pain is a problem with various interacting components, that requires characterization at a systems level (Fig. 1) (Mao, 2012). This calls for the use of quantitative systems pharmacology (QSP), a rapidly emerging discipline that combines concepts from both systems biology and PK-PD modelling (Vicini and van der Graaf, 2013). QSP approaches enable the comprehensive characterization of pain and its underlying pharmacological, physiological and psychological processes. Because biomarkers can give us insight into these processes, they play a key role in characterizing the variability and interactions of the system components of pain and treatment response (Danhof, 2016). With an integrative understanding of the variability in the system of pain, we can arguably improve our ability to deliver personalized treatment, compared to approaches that focus on a single component of the pain (e.g., only pharmacokinetics or only psychology).

Molecular and imaging-based biomarkers can inform mechanistic details related to QSP models of pain, because they inform us about underlying physiological processes (Danhof et al., 2005). This could contribute to more mechanistic characterization of drug exposure-response relationships, and potentially be used to predict or monitor inter-individual variability in treatment response. QSP models might also facilitate development of novel biomarkers by providing a framework for their quantitative interpretation. The quantitative understanding of biomarkers and their relation to pain and treatment response is crucial if they are to be incorporated in personalized

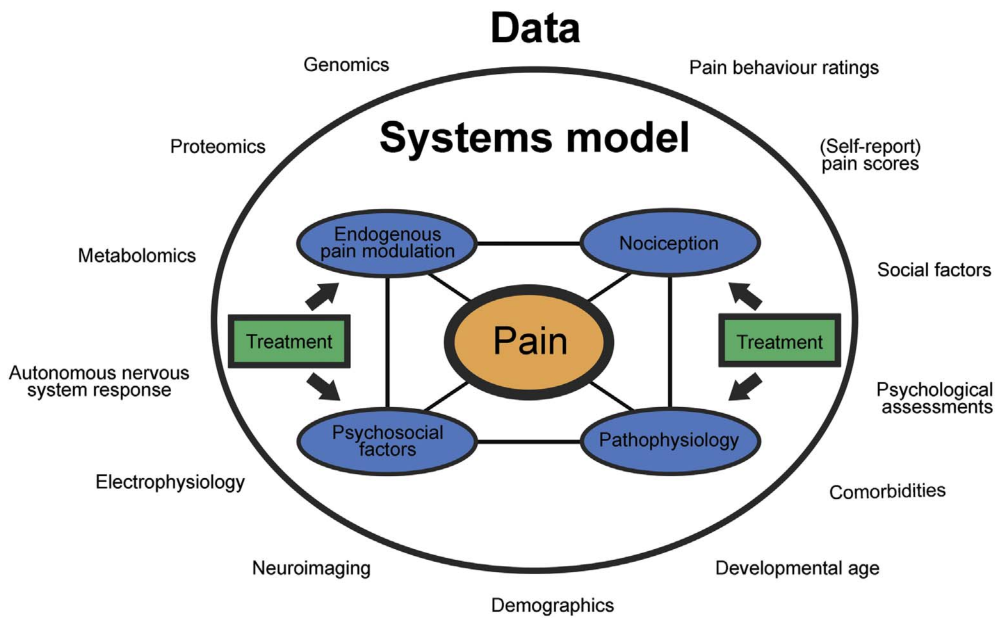

Fig. 1. Systems view of the complexity and connectivity of clinical pain. A systems understanding of pain relies on a mechanistic understand of its underlying processes. Data types which can provide information on this understanding include patient-reported outcomes, psychological assessments, neuroimaging and molecular markers, of which examples are shown.

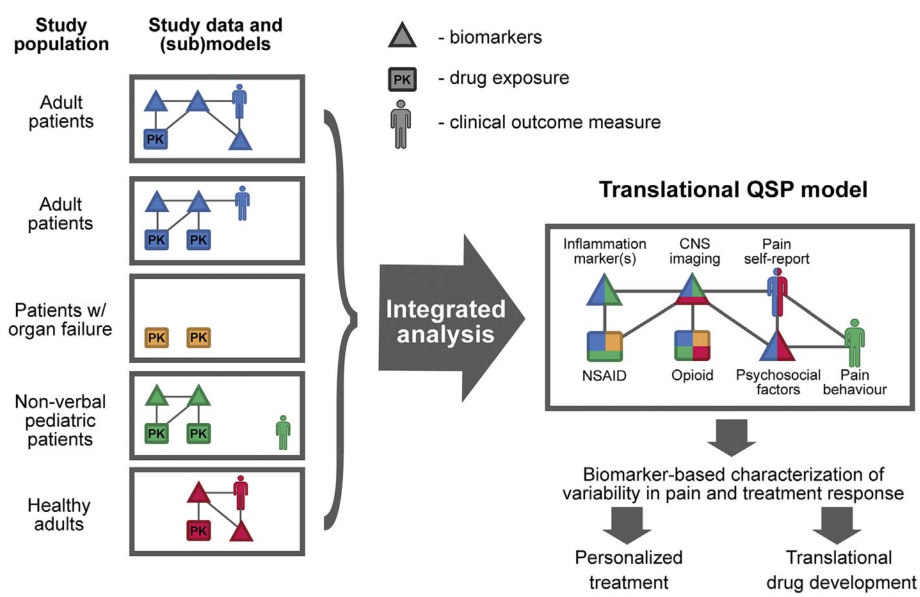

Fig. 2. Integration of data from different populations within a translational quantitative systems pharmacology (QSP) model to support personalized treatment and drug development. CNS, central nervous system.

treatment approaches.

By moving from empiricism to mechanism, QSP approaches have improved properties for translation and prediction (Vicini and van der Graaf, 2013). These improved translational properties can enable the simultaneous analysis of multiple clinical studies in comparable pain conditions. Fig. 2 illustrates the concept of integrated analysis of data from different patient populations to develop a translational QSP model. Being able to translate findings and biomarkers across different patient populations, would be especially beneficial in patient populations that are unable of self-reporting pain. This translation will by no means be a trivial task, as there are differences in many of the underlying components of pain and treatment response in these populations. For example, the neurophysiological component of pain differs between neonates and adults (Fitzgerald, 2015). The success of these translational efforts will likely depend on our ability to take these differences into account. Moreover, it will be difficult to validate model-based personalized medicine approaches in populations without self-report, because behavioural pain scales do not provide a direct measure of pain perception (Herr et al., 2011). However, we would argue that mechanism-based models and biomarkers have a greater potential for personalized treatment in these populations than more empirical counterparts.

The proposed QSP approach will be of relevance to drug development as well. These models might help to identify and validate new drug targets, or suggest suitable combinations of existing drugs (Sorger et al., 2011). In drug development, QSP models would provide a better basis for the prediction of optimal dose regimens and translation (e.g., preclinical to clinical or between different human populations) (Vicini and van der Graaf, 2013). Finally, the biomarkers originating from this QSP approach might be used to improve the translational performance of preclinical pain models.

To develop QSP models of pain, data is required that informs on the underlying processes of pain. Some of the required data might be obtained from previously conducted studies, underlining the need for increased collaboration and data-sharing in both industry and academia (Ince et al., 2009; Romero et al., 2010). Recent initiative to promote these public-private partnerships include the European Innovative Medicines Initiative (IMI), which has issued a call for project applications aiming to improve the translatability of pharmacodynamic biomarkers in pain pathways from healthy subjects and preclinical models (Innovative Medicines Initiative, 2016). To allow characterization of the interactions of the systems components, future studies would ideally quantify multiple biomarkers and potential predictors of pain in the same patients: pain self-report, imaging/EEG-based markers, biomarker profiles in blood, psychosocial factors, drug exposure, etc. Pain studies in healthy volunteers can complement information from clinical studies, as they allow the study of separate system components in a highly controlled setting (Lee and Tracey, 2013). However, the level of psychological distress and type of noxious stimuli will differ from a clinical setting. Finally, continued development in preclinical models such as organ-on-a-chip might also contribute to systems models by allowing the study of isolated processes in a controlled setting (Barrett and Haas, 2016).

5. Summary

Clinical pain is a complex and multifactorial phenomenon that has multiple physiological and psychosocial components. This complexity has hindered our understanding of clinical pain, the search for predictors of inter-individual variation in pain and treatment response, and the identification of novel biomarkers for pain in patients unable to self-report pain. We propose that a QSP approach will contribute towards a quantitative understanding of the various interacting components that underlie the variability in pain and treatment response. Secondly, QSP approaches can complement molecular profiling techniques such as metabolomics, in the search and development of novel biomarkers. Therefore, QSP approaches will likely improve our ability to predict pain and treatment response, paving the way for personalized treatment of pain.

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References

Amanzio, M., Pollo, A., Maggi, G., Benedetti, F., 2001. Response variability to analgesics: a role for non-specific activation of endogenous opioids. Pain 90, 205–215.
Anderson, B.J., Woollard, G.A., Holford, N.H., 2001. Acetaminophen analgesia in children: placebo effect and pain resolution after tonsillectomy. Eur. J. Clin. Pharmacol. 57, 559–569.
Apfelbaum, J.L., Chen, C., Mehta, S.S., Gan, T.J., 2003. Postoperative pain experience: results from a National Survey Suggest Postoperative Pain Continues to be undermanaged. Anesth. Analg. 97, 534–540.
Arnstein, P., Broglio, K., Wuhrman, E., Kean, M.B., 2011. Use of placebos in pain management. Pain Manag. Nurs. 12, 225–229.
Aubrun, F., Mazoit, J.X., Riou, B., 2012. Postoperative intravenous morphine titration. Br. J. Anaesth. 108, 193–201.
Baarslag, M.A., Allegaert, K., van den Anker, J.N., Knibbe, C.A., van D, M., Simons, S.H., Tibboel, D., 2017. Paracetamol and morphine for infant and neonatal pain; still a long way to go? Expert. Rev. Clin. Pharmacol. 10, 111–126.
Backryd, E., 2015. Pain in the blood? Envisioning mechanism-based diagnoses and biomarkers in clinical pain medicine. Diagnostics 5, 84–95 (Basel).
Backryd, E., Ghafouri, B., Larsson, B., Gerdle, B., 2014. Do low levels of Beta-endorphin in the cerebrospinal fluid indicate defective top-down inhibition in patients with chronic neuropathic pain? A cross-sectional, comparative study. Pain Med. 15, 111–119.
Baliki, M.N., Petre, B., Torbey, S., Herrmann, K.M., Huang, L., Schnitzer, T.J., Fields, H.L., Apkarian, A.V., 2012. Corticostriatal functional connectivity predicts transition to chronic back pain. Nat. Neurosci. 15, 1117–1119.
Barrett, J.E., Haas, D.A., 2016. Perspectives and Trends in Pharmacological Approaches to the Modulation of Pain. In: Barrett, J.E. (Ed.), Pharmacological Mechanisms and the Modulation of Pain. Elsevier Science, pp. 27–33.
Beger, R.D., Dunn, W., Schmidt, M.A., Gross, S.S., Kirwan, J.A., Cascante, M., Brennan, L., Wishart, D.S., Oresic, M., Hankemeier, T., Broadhurst, D.I., Lane, A.N., Suhre, K., Kastenmuller, G., Sumner, S.J., Thiele, I., Fiehn, O., Kaddurah-Daouk, R., 2016. Metabolomics enables Precision medicine: "a white paper, community perspective". Metabolomics 12, 149.
Bingel, U., Wanigasekera, V., Wiech, K., Ni, M.R., Lee, M.C., Ploner, M., Tracey, I., 2011. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid Remifentanil. Sci. Transl. Med. 3, 70ra14.
Bjornsson, M.A., Simonsson, U.S., 2011. Modelling of pain intensity and informative dropout in a dental pain model after Naproxcinod, naproxen and placebo administration. Br. J. Clin. Pharmacol. 71, 899–906.
Borsook, D., Becerra, L., 2011. How close are we in utilizing functional neuroimaging in routine clinical diagnosis of neuropathic pain? Curr. Pain Headache Rep. 15, 223–229.
Borsook, D., Becerra, L., Hargreaves, R., 2011. Biomarkers for chronic pain and analgesia. Part 1: the need, reality, Challenges, and solutions. Discov. Med. 11, 197–207.
Breimer, D.D., Danhof, M., 1997. Relevance of the application of pharmacokinetic-Pharmacodynamic Modelling concepts in drug development. The “Wooden Shoe” paradigm. Clin. Pharmacokinet. 32, 259–267.
Byon, W., Ouellet, D., Chew, M., Ito, K., Burger, P., Pauer, L., Zeiher, B., Corrigan, B., 2010. Exposure-response analyses of the effects of Pregabalin in patients with fibromyalgia using daily pain scores and patient global impression of change. J. Clin. Pharmacol. 50, 803–815.
Chen, R., Snyder, M., 2013. Promise of personalized Omics to Precision medicine. Wiley Interdiscip. Rev. Syst. Biol. Med. 5, 73–82.
Chizh, B.A., Greenspan, J.D., Casey, K.L., Nemenov, M.I., Treede, R.D., 2008. Identifying biological markers of activity in human nociceptive pathways to facilitate analgesic drug development. Pain 140, 249–253.
Colloca, L., Klinger, R., Flor, H., Bingel, U., 2013. Placebo analgesia: psychological and neurobiological Mechanisms. Pain 154, 511–514.
Cowen, R., Stasiowska, M.K., Laycock, H., Bantel, C., 2015. Assessing pain objectively: the use of physiological markers. Anaesthesia 70, 828–847.
Danhof, M., 2016. Systems pharmacology - towards the Modeling of network interactions. Eur. J. Pharm. Sci. 94, 4–14.
Danhof, M., Alvan, G., Dahl, S.G., Kuhlmann, J., Paintaud, G., 2005. Mechanism-based pharmacokinetic-Pharmacodynamic Modeling-a new classification of biomarkers. Pharm. Res. 22, 1432–1437.
Danhof, M., de Jongh, J., de Lange, E.C., Della, P.O., Ploeger, B.A., Voskuyl, R.A., 2007. Mechanism-based pharmacokinetic-Pharmacodynamic Modeling: Biophase distribution, receptor theory, and dynamical systems analysis. Annu. Rev. Pharmacol. Toxicol. 47, 357–400.
Davis, K.D., Racine, E., Collett, B., 2012. Neuroethical issues related to the use of brain imaging: can we and should we use brain imaging as a biomarker to diagnose chronic pain? Pain 153, 1555–1559.
van Dijk, M., de Boer, J.B., Koot, H.M., Tibboel, D., Passchier, J., Duivenvoorden, H.J., 2000. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. Pain 84, 367–377.
Fillingim, R.B., Hastie, B.A., Ness, T.J., Glover, T.L., Campbell, C.M., Staud, R., 2005. Sex-related psychological predictors of baseline pain perception and analgesic responses to Pentazocine. Biol. Psychol. 69, 97–112.
Fitzgerald, M., 2015. What do we really know about newborn infant pain? Exp. Physiol. 100, 1451–1457.
Frank, R., Hargreaves, R., 2003. Clinical biomarkers in drug discovery and development. Nat. Rev. Drug Discov. 2, 566–580.
Gil, K.M., Ginsberg, B., Muir, M., Sykes, D., Williams, D.A., 1990. Patient-controlled analgesia in postoperative pain: the relation of psychological factors to pain and analgesic use. Clin. J. Pain 6, 137–142.
Gilron, I., Jensen, T.S., Dickenson, A.H., 2013. Combination pharmacotherapy for Management of Chronic Pain: from bench to bedside. Lancet Neurol. 12, 1084–1095.
Gram, M., Erlenwein, J., Petzke, F., Falla, D., Przemeck, M., Emons, M.I., Reuster, M., Olesen, S.S., Drewes, A.M., 2017. Prediction of postoperative opioid analgesia using clinical-experimental parameters and electroencephalography. Eur. J. Pain 21, 264–277.
Hartley, C., Duff, E.P., Green, G., Mellado, G.S., Worley, A., Rogers, R., Slater, R., 2017. Nociceptive brain activity as a measure of analgesic efficacy in infants. Sci. Transl. Med. 9, eaah6122.
Haythornthwaite, J.A., Clark, M.R., Pappagallo, M., Raja, S.N., 2003. Pain coping strategies play a role in the persistence of pain in Post-herpetic neuralgia. Pain 106, 453–460.
van Herk, R., van Dijk, M., Tibboel, D., Baar, F.P., de Wit, R., Duivenvoorden, H.J., 2009. The Rotterdam elderly pain observation scale (REPOS): a new behavioral pain scale for non-communicative adults and cognitively impaired elderly persons. J. Pain. Manage. 1, 367–378.
Herr, K., Coyne, P.J., McCaffery, M., Manworren, R., Merkel, S., 2011. Pain assessment in the patient unable to self-report: position statement with clinical practice recommendations. Pain Manag. Nurs. 12, 230–250.
Hinrichs-Rocker, A., Schulz, K., Jarvinen, I., Lefering, R., Simanski, C., Neugebauer, E.A., 2009. Psychosocial predictors and correlates for chronic Post-surgical pain (CPSP) - a Systematic review. Eur. J. Pain 13, 719–730.
Hodkinson, D.J., Khawaja, N., O'Daly, O., Thacker, M.A., Zelaya, F.O., Wooldridge, C.L., Renton, T.F., Williams, S.C., Howard, M.A., 2015. Cerebral analgesic response to Nonsteroidal anti-inflammatory drug ibuprofen. Pain 156, 1301–1310.
Huang, G., Xiao, P., Hung, Y.S., Iannetti, G.D., Zhang, Z.G., Hu, L., 2013. A novel approach to predict subjective pain perception from single-trial laser-evoked potentials. NeuroImage 81, 283–293.
Huntjens, D.R., Danhof, M., Della Pasqua, O.E., 2005. Pharmacokinetic-

Pharmacodynamic correlations and biomarkers in the development of COX-2 inhibitors. Rheumatology (Oxford) 44, 846–859.
Ince, I., de Wildt, S.N., Tibboel, D., Danhof, M., Knibbe, C.A., 2009. Tailor-made drug treatment for children: creation of an infrastructure for data-sharing and population PK-PD Modeling. Drug Discov. Today 14, 316–320.
Innovative Medicines Initiative, 2016. Future topics for IMI2 - Call 10: Improving the care of patients suffering from actue or chronic pain. Available at: https://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/imi2-2016-10-03.html.
Ip, H.Y., Abrishami, A., Peng, P.W., Wong, J., Chung, F., 2009. Predictors of postoperative pain and analgesic consumption: a qualitative Systematic review. Anesthesiology 111, 657–677.
Iskandar, H.N., Ciorba, M.A., 2012. Biomarkers in inflammatory bowel disease: Current practices and Recent advances. Transl. Res. 159, 313–325.
Ji, R.R., Chamessian, A., Zhang, Y.Q., 2016. Pain regulation by non-neuronal cells and inflammation. Science 354, 572–577.
Juul, R.V., Nyberg, J., Lund, T.M., Rasmussen, S., Kreilgaard, M., Christrup, L.L., Simonsson, U.S., 2016. A pharmacokinetic-Pharmacodynamic model of morphine exposure and subsequent morphine consumption in postoperative pain. Pharm. Res. 33, 1093–1103.
Kerns, R.D., Turk, D.C., Rudy, T.E., 1985. The West Haven-Yale multidimensional pain inventory (WHYMPI). Pain 23, 345–356.
Kilts, J.D., Tupler, L.A., Keefe, F.J., Payne, V.M., Hamer, R.M., Naylor, J.C., Calnaido, R.P., Morey, R.A., Strauss, J.L., Parke, G., Massing, M.W., Youssef, N.A., Shampine, L.J., Marx, C.E., 2010. Neurosteroids and self-reported pain in veterans who served in the U.S. military after September 11, 2001. Pain Med. 11, 1469–1476.
Kohler, I., Hankemeier, T., van der Graaf, P.H., Knibbe, C.A.J., van Hasselt, J.G.C., 2017. Integrating clinical metabolomics-based biomarker discovery and clinical pharmacology to enable Precision medicine. Eur. J. Pharm. Sci (this issue).
Komatsu, T., Kokubun, H., Suzuki, A., Takayanagi, R., Yamada, Y., Matoba, M., Yago, K., 2012. Population pharmacokinetics of oxycodone in patients with cancer-related pain. J. Pain Palliat. Care Pharmacother. 26, 220–225.
Krekels, E.H., Tibboel, D., de Wildt, S.N., Ceelie, I., Dahan, A., van D, M., Danhof, M., Knibbe, C.A., 2014. Evidence-based morphine dosing for postoperative neonates and infants. Clin. Pharmacokinet. 53, 553–563.
Lame, I.E., Peters, M.L., Vlaeyen, J.W., Kleef, M., Patijn, J., 2005. Quality of life in chronic pain is more associated with beliefs about pain, than with pain intensity. Eur. J. Pain 9, 15–24.
Lee, M.C., Tracey, I., 2013. Imaging pain: a potent means for investigating pain Mechanisms in patients. Br. J. Anaesth. 111, 64–72.
Lee, M.C., Wanigasekera, V., Tracey, I., 2014. Imaging opioid analgesia in the human brain and its potential relevance for understanding opioid use in chronic pain. Neuropharmacology 84, 123–130.
Linton, S.J., Shaw, W.S., 2011. Impact of psychological factors in the experience of pain. Phys. Ther. 91, 700–711.
Mao, J., 2012. Current Challenges in translational pain research. Trends Pharmacol. Sci. 33, 568–573.
Martini, C., Olofsen, E., Yassen, A., Aarts, L., Dahan, A., 2011. Pharmacokinetic-Pharmacodynamic Modeling in acute and chronic pain: an overview of the Recent literature. Expert. Rev. Clin. Pharmacol. 4, 719–728.
Masselin-Dubois, A., Attal, N., Fletcher, D., Jayr, C., Albi, A., Fermanian, J., Bouhassira, D., Baudic, S., 2013. Are psychological predictors of chronic postsurgical pain dependent on the surgical model? A comparison of Total knee Arthroplasty and breast surgery for cancer. J. Pain 14, 854–864.
Mazoit, J.X., Butscher, K., Samii, K., 2007. Morphine in postoperative patients: pharmacokinetics and pharmacodynamics of metabolites. Anesth. Analg. 105, 70–78.
McArdle, A., Flatley, B., Pennington, S.R., FitzGerald, O., 2015. Early biomarkers of joint damage in rheumatoid and psoriatic arthritis. Arthritis Res. Ther. 17, 141.
McCaffery, M., 1968. Nursing Practice Theories Related to Cognition, Bodily Pain, and Man-Environment Interactions. UCLA Students' Store, Los Angeles, California.
Melzack, R., 2001. Pain and the Neuromatrix in the brain. J. Dent. Educ. 65, 1378–1382.
Merskey, H., Bogduk, N., 1994. Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definition of Pain Terms. International Association for the Study of Pain Press, Seattle.
Mogil, J.S., 2012. Pain genetics: past, present and future. Trends Genet. 28, 258–266.
Mould, D.R., Lesko, L.J., 2014. Personalized medicine: integrating individual exposure and response information at the bedside. In: Schmidt, S., Derendorf, H. (Eds.), Applied Pharmacometrics. York, Springer-Verlag New, pp. 65–82.
Mould, D.R., Upton, R.N., 2012. Basic concepts in population Modeling, simulation, and model-based drug development. CPT Pharmacom. Syst. Pharmacol. 1, e6.
Oertel, B.G., Preibisch, C., Wallenhorst, T., Hummel, T., Geisslinger, G., Lanfermann, H., Lotsch, J., 2008. Differential opioid action on sensory and affective Cerebral pain processing. Clin. Pharmacol. Ther. 83, 577–588.
Pasero, C., McCaffery, M., 2005. No self-report means no pain-intensity rating. Am. J. Nurs. 105, 50–53.
Pinheiro, E.S., de Queiros, F.C., Montoya, P., Santos, C.L., do Nascimento, M.A., Ito, C.H., Silva, M., Nunes Santos, D.B., Benevides, S., Miranda, J.G., Sa, K.N., Baptista, A.F., 2016. Electroencephalographic patterns in chronic pain: a Systematic review of the literature. PLoS One 11, e0149085.
Quartana, P.J., Campbell, C.M., Edwards, R.R., 2009. Pain Catastrophizing: a critical review. Expert. Rev. Neurother. 9, 745–758.
Quartana, P.J., Buenaver, L.F., Edwards, R.R., Klick, B., Haythornthwaite, J.A., Smith, M.T., 2010. Pain Catastrophizing and salivary cortisol responses to laboratory pain testing in Temporomandibular disorder and healthy participants. J. Pain 11, 186–194.
Reicherts, P., Gerdes, A.B., Pauli, P., Wieser, M.J., 2016. Psychological placebo and Nocebo effects on pain rely on expectation and previous experience. J. Pain 17, 203–214.
Rogers, W.H., Wittink, H., Wagner, A., Cynn, D., Carr, D.B., 2000. Assessing individual outcomes during outpatient multidisciplinary chronic pain treatment by means of an augmented SF-36. Pain Med. 1, 44–54.
Romero, K., Corrigan, B., Tornoe, C.W., Gobburu, J.V., Danhof, M., Gillespie, W.R., Gastonguay, M.R., Meibohm, B., Derendorf, H., 2010. Pharmacometrics as a discipline is entering the "industrialization" phase: standards, automation, knowledge sharing, and training are critical for future success. J. Clin. Pharmacol. 50, 9S–19S.
Russell, E., Koren, G., Rieder, M., Van, U.S., 2012. Hair cortisol as a biological marker of chronic stress: Current status, future directions and unanswered questions. Psychoneuroendocrinology 37, 589–601.
Sava, S., Lebel, A.A., Leslie, D.S., Drosos, A., Berde, C., Becerra, L., Borsook, D., 2009. Challenges of functional imaging research of pain in children. Mol. Pain 5, 30.
Schweinhardt, P., Bushnell, M.C., 2010. Pain imaging in health and disease–how far have we come? J. Clin. Invest. 120, 3788–3797.
Sorger, P.K., Allerheiligen, S.R.B., Abernethy, D.R., Altman, R.B., Brouwer, K.L.R., Califano, A., D'Argenio, D.Z., Iyengar, R., Jusko, W.J., Lalonde, R., Lauffenburger, D.A., Shoichet, B., Stevens, J.L., Subramanian, S., van der Graaf, P.H., Vicini, P., 2011. Quantitative and Systems Pharmacology in the Post-genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms. Available at: https://www.nigms.nih.gov/Training/Documents/SystemsPharmaWPSorger2011.pdf.
Sturgeon, J.A., Zautra, A.J., 2013. Psychological resilience, pain Catastrophizing, and positive emotions: perspectives on comprehensive Modeling of individual pain adaptation. Curr. Pain Headache Rep. 17, 317.
Sullivan, M.J.L., Bishop, S., Pivik, J., 1995. The pain Catastrophizing scale: development and validation. Psychol. Assess. 7, 524–532.
Symons, F.J., ElGhazi, I., Reilly, B.G., Barney, C.C., Hanson, L., Panoskaltsis-Mortari, A., Armitage, I.M., Wilcox, G.L., 2015. Can biomarkers differentiate pain and no pain subgroups of nonverbal children with Cerebral palsy? A preliminary investigation based on noninvasive saliva sampling. Pain Med. 16, 249–256.
Taneja, A., Oosterholt, S.P., Danhof, M., Della Pasqua, O., 2016. Biomarker exposure-response relationships as the basis for rational dose selection: lessons from a simulation exercise using a selective COX-2 inhibitor. J. Clin. Pharmacol. 56, 609–621.
Vardeh, D., Mannion, R.J., Woolf, C.J., 2016. Toward a mechanism-based approach to pain diagnosis. J. Pain 17, T50–T69.
Vicini, P., van der Graaf, P.H., 2013. Systems pharmacology for drug discovery and development: paradigm shift or flash in the pan? Clin. Pharmacol. Ther. 93, 379–381.
Warden, V., Hurley, A.C., Volicer, L., 2003. Development and psychometric evaluation of the pain assessment in advanced dementia (PAINAD) scale. J. Am. Med. Dir. Assoc. 4, 9–15.
Wiech, K., 2016. Deconstructing the sensation of pain: the influence of cognitive processes on pain perception. Science 354, 584–587.
Wishart, D.S., 2016. Emerging applications of metabolomics in drug discovery and Precision medicine. Nat. Rev. Drug Discov. 15, 473–484.
Younger, J., McCue, R., Mackey, S., 2009. Pain outcomes: a brief review of instruments and techniques. Curr. Pain Headache Rep. 13, 39–43.