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REVIEW

Clinical pharmacology of analgesics assessed with human experimental pain models: bridging basic and clinical research

Bruno Georg Oertel[1,2] and Jörn Lötsch[2]

[1]*Fraunhofer Project Group Translational Medicine and Pharmacology (IME-TMP), Frankfurt am Main, Germany, and* [2]*Institute of Clinical Pharmacology, Goethe – University, Frankfurt am Main, Germany*

Correspondence
Prof Dr Jörn Lötsch, *pharmazentrum frankfurt*/ZAFES, Institute of Clinical Pharmacology, J. W. Goethe-University, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany. E-mail: j.loetsch@em.uni-frankfurt.de

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The medical impact of pain is such that much effort is being applied to develop novel analgesic drugs directed towards new targets and to investigate the analgesic efficacy of known drugs. Ongoing research requires cost-saving tools to translate basic science knowledge into clinically effective analgesic compounds. In this review we have re-examined the prediction of clinical analgesia by human experimental pain models as a basis for model selection in phase I studies. The overall prediction of analgesic efficacy or failure of a drug correlated well between experimental and clinical settings. However, correct model selection requires more detailed information about which model predicts a particular clinical pain condition. We hypothesized that if an analgesic drug was effective in an experimental pain model and also a specific clinical pain condition, then that model might be predictive for that particular condition and should be selected for development as an analgesic for that condition. The validity of the prediction increases with an increase in the numbers of analgesic drug classes for which this agreement was shown. From available evidence, only five clinical pain conditions were correctly predicted by seven different pain models for at least three different drugs. Most of these models combine a sensitization method. The analysis also identified several models with low impact with respect to their clinical translation. Thus, the presently identified agreements and non-agreements between analgesic effects on experimental and on clinical pain may serve as a solid basis to identify complex sets of human pain models that bridge basic science with clinical pain research.

Introduction

Pain is the most frequent reason for visiting a doctor. Large-scale studies in Western countries have shown that a fifth of the adult population suffer from chronic pain (http://www.iasp-pain.org). Despite several available analgesics, unrelieved pain remains a major health care issue. For example, in the USA the annual cost for medical treatment and lost productivity due to pain is 635 billion US$ (Committee on Advancing Pain Research, 2011). The current strategies of the pharmaceutical industry for analgesic drug development include (i) reformulations of known substances, (ii) repurposing of known drugs to address new indications and patient populations and (iii) the development of new drugs with novel mechanisms of action. The immense costs of these development efforts need to be limited by strategies that allow the prediction of clinical success without the need for large clinical trials.

Experimental pain models have been established as cost-effective tools for assessing analgesic drug efficacy. However, their translation into new clinically effective compounds seems to be unsatisfactory (Mogil, 2009). The prediction of clinical efficacy of analgesics obtained in human pain models has not been reviewed in this manner and there is no

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immediate reason why they would be better than animal models. This assessment is a prerequisite to fully exploit the cost-saving potential of experimental methods in analgesic drug development. It can be based on knowledge about analgesic drug effects in both, experimental and clinical settings.

As a basis of this review, we hypothesized that if an analgesic drug was effective in an experimental model and also in a clinical setting, then the experimental model might be predictive for the particular clinical setting. For example, from the observations that pregabalin was effective in neuropathic pain treatment (Moore *et al.*, 2009j) and reduced experimental cold pain thresholds (Altis *et al.*, 2009), experimental cold pain could be used to predict whether a drug will also be an effective analgesic for clinical neuropathic pain. Therefore, in the present review we have analysed the information about efficacies of analgesic drugs in both human experimental models and clinical assessments to establish probable predictive relationships as model selection guidance and to direct future developments of predictive human pain models.

Classical and new analgesic drugs tested experimentally and clinically

Increasingly severe chronic pain is treated according to the stepladder of the World Health Organization for the treatment of cancer pain (http://www.who.int/cancer/palliative/painladder/en/). This guides the selection (Table 1) of increasingly potent analgesics ranging from non-opioid (e.g. classical NSAIDs non-selectively inhibiting COXs, selective COX-2 inhibitors, paracetamol, metamizol), via so-called weak opioids (e.g. codeine, dihydrocodeine, tramadol, tilidine) to highly potent opioids (e.g. morphine, fentanyl, buprenorphine). The main target of most of the clinically available opioids is the μ-opioid receptor; however, they also bind to other opioid receptors but with comparatively low binding affinity (Emmerson *et al.*, 1994), with a few exceptions κ-opioid agonists (e.g. pentazocine, nalbuphine, butorphanol, levallorphan and norbinaltorphine) are of fading clinical importance. Further classical analgesics include flupirtine, an activator of G-protein coupled inwardly rectifying K^+ channels (Kornhuber *et al.*, 1999), cannabinoids, which activate cannabinoid CB_1 and CB_2 receptors and are an approved for the treatment of multiple-sclerosis-associated neuropathic pain, and several NMDA ion channel antagonists such as ketamine (Smothers and Woodward, 2007). Co-analgesics are primarily used for clinical indications other than pain relief but have demonstrated analgesic effects in particular pain conditions such as neuropathic pain. This includes anti-epileptic drugs such as pregabalin and gabapentin, which modulate the $\alpha_2\delta$ subunit of L-type voltage-gated calcium channels (Field *et al.*, 2006); carbamazepine and lamotrigin, which modulate the voltage-gated sodium channel subunits $Na_v1.5$ and $Na_v1.2$ (Lipkind and Fozzard, 2005; Yang *et al.*, 2010), respectively; and tricyclic or heterocyclic antidepressants that increase noradrenergic and 5-hydroxytryptaminergic neuronal signalling by inhibiting transmitter re-uptake and inhibit sodium channels (Dick *et al.*, 2007).

The recognition of chronic pain as a major public health care problem has triggered the development of new analgesics (Table 1), which so far has led to several new substances being approved, such as the N-type voltage-gated calcium channel inhibitor ziconotide (Miljanich, 2004), or currently being tested in clinical trials. Using publicly available sources of information (http://www.clinicaltrials.gov, company websites, presentations and press releases), several new analgesic drug targets have been revealed (Lotsch and Geisslinger, 2011), such as various transient receptor potential (Patapoutian *et al.*, 2009), sodium (Clare, 2010) and calcium channels (Schmidtko *et al.*, 2010).

Efficacy of analgesic drugs

Due to the complexity of pain with many different molecular components and pathways (Julius and Basbaum, 2001), clinical pain displays a pattern of different phenotypes for which different analgesics provide therapies of varying success. Choosing the right analgesic for a particular pain in an individual patient is a major therapeutic challenge. Therefore, the efficacy of analgesic drugs has been assessed separately for various clinical settings and by different experimental models. This has produced a complex pattern of drug efficacies for particular pain conditions.

Efficacy of analgesics on clinical pain

Classifications of clinical pain. Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or is described in terms of such damage (International Association for the Study of Pain, IASP, at http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions#Pain). Pain is thus primarily a biological warning system, which becomes evident from the severe pathologies associated with complete insensitivity to pain in patients with familial syndromes of hereditary autonomic and sensory neuropathies (Oertel and Lötsch, 2008). When pain loses its warning function or chronifies, it becomes a disease requiring treatment. A simple classification based on pain duration distinguishes acute and chronic pain. However, this classification is unsatisfactory as a basis for individualized clinical analgesia and is therefore not suitable for drug development. Alternative classifications provide better guidance, such as the differentiation of nociceptive, neuropathic and mixed pain (Basbaum *et al.*, 2009; Woolf, 2010). However, these classifications are not precise enough to address individual pain settings. Therefore, in the present report we have used the classification of pain used for the analysis of analgesic efficacy stored in the Cochrane library (http://www.thecochranelibrary.com). This detailed classification of clinical pain conditions (Table 2) was considered to be the best basis for drug development targeted at particular populations of pain patients.

Search strategy. A Cochrane library search for 'pain' in July 2012 yielded 1161 hits, from which 35 clinical pain conditions were identified (Table 2). These settings were considered to adequately reflect the majority of clinical targets of analgesic drugs. To identify drugs tested for their analgesic

Table 1

Classes of analgesic drugs including classical analgesics, several new analgesics for which evidence for both clinical and experimental efficacy were available, and so-called co-analgesics

Drug class		Drugs	Pharmacological targets	Gene	Action
Opioids	Opioids (strong)	Morphine, hydromorphon, oxycodone, alfentanil, fentanyl, buprenorphine, etc.	Opioid receptors μ, κ, δ	*OPRM1, OPRK1, OPRD1*	Agonist
	Opioids (weak)	Tramadol, codeine, dihydrocodeine, tillidine	Opioid receptors μ, κ, δ	*OPRM1, OPRK1, OPRD1*	Agonist
Non-opioid analgesics	NSAIDs	Acetylsalicylic acid, ibuprofen, naproxen, diclofenac, indometacine	COX-1 /-2	*PTGS1, PTGS2*	Inhibitor
	NSAIDs	Dipyrone	COX-1 /-2 and others	*PTGS1, PTGS2 and others*	Inhibitor
	NSAIDs	Paracetamol	COX-1 /-2 and others	*PTGS1, PTGS2 and others*	Inhibitor
	COX-2 inhibitors	Celecoxib, lumiracoxib, etoricoxib	COX-2	*PTGS2*	Inhibitor
	KCNQ/Kv7 potassium channels activator/inhibitor	Flupirtine	KCNQ/K_v7 potassium channels	*KCNQ2, KCNQ3*	Activator/ Inhibitor
	TRPV1 agonist	Capsaicin	Transient receptor potential channels TRPV1	*TRPV1*	Agonist
	TRPV1 antagonist	AZD-1386	Transient receptor potential channels TRPV1	*TRPV1*	Antagonist
	NMDA rec. antagonists	Ketamine	NMDA ion channel subtype NR3A	*GRIN3A*	Antagonist
	Cannabinoids	Cannabis, Δ^9-tetrahydrocannabinol	Cannabinoid receptor 1 (CB_1), Cannabinoid receptor 2 (CB_2)	*CNR1, CNR2*	Agonist
Co-analgesics	Antiepileptics	Carbamazepine	Voltage-gated sodium channel subunit α $Na_v1.5$	*SCN5A*	Inhibitor
	Antiepileptics	Pregabalin	Voltage-dependent calcium channel subunit α2δ	*CACNA2D1*	Inhibitor
	Antiepileptics	Gabapentin	Voltage-dependent calcium channel subunit α2δ	*CACNA2D1*	Inhibitor
	Antiepileptics	Lamotrigin	Voltage-gated sodium channel subunit α $Na_v1.2$	*SCN2A*	Inhibitor
	Antidepressants	Tri-/tetracyclics (e.g. maprotiline, nortriptyline, amitriptyline)	Sodium-dependent noradrenaline transporter, histamine H_1 receptor, Muscarinic acetylcholine receptor $M_{1/2/3/4/5}$, α_{1A} adrenoceptor	*SLC6A2, HRH1, CHRM1/2/3/4/5, ADRA1A*	Inhibitor/ Antagonist
Others	Benzodiazepines	Clonazepam, diazepam	GABA receptors	*GABR*	Potentiator
	Centrally acting α_2-adrenoceptor agonist	Clonidine	$\alpha_{2A/2B/2C}$ adrenoceptor	*ADRA2A, ADRA2B, ADRA2C*	Agonist

Their pharmacological targets and the genes coding for these targets and the effect on the target are also given. In addition, benzodiazepines and the α_2 adrenoceptor agonist clonidine are listed as their analgesic effects have been assessed analogously.

Table 2

Clinical pain conditions as described in *The Cochrane library* (sorted alphabetically) (http://www.thecochranelibrary.com)

Clinical pain condition	Description
Acute abdominal pain	One of the top three symptoms in the emergency room (5% and 10% of all the illnesses treated in the ED); commonly caused by appendicitis, cholecystitis, intestinal obstruction, urinary colic, gastritis, perforated peptic ulcer, gastroenteritis, pancreatitis, diverticulitis, gynaecological disorders in women and non-surgical abdominal pain
Acute migraine	Disabling headache disorder, affecting about 12% of Western populations; more prevalent in women than men (on the order of 18% vs. 6% 1-year prevalence), and in the age range 30 to 50 years
Atypical facial pain	Syndrome encompassing a wide group of facial pain problems including continuous burning, aching or cramping; occurs on one side of the face, often in the region of the trigeminal nerve and can extend into the upper neck or back of the scalp; few, if any periods of remission
Burn injury	See trauma
Burning mouth syndrome	Burning sensation on the lips, tongue or within the mouth; mouth dryness, altered taste; Cause: unknown; women after menopause are at highest risk; common in people with anxiety, depression and personality disorders
Cancer pain	Caused by the disease itself or by treatments
Central neuropathic	Conditions arising from injury or disease of the CNS, such as spinal cord injury (SCI), syringomyelia, multiple sclerosis (MS), stroke (infarction or haemorrhage), traumatic brain injury, Parkinson's disease, tumours and epilepsy
Chemotherapy induced	See cancer pain
Child birth/labour	Painful intermittent, accompanying uterine contractions
Diabetic neuropathy	Nerve damage due to high blood sugar levels mostly affecting nerves in legs and feet; symptoms ranging from mild to disabling to even fatal
Dysmenorrhoea (prim.)	Painful cramps accompanying menstruation; high levels of prostaglandins and hormones known to cause cramping abdominal pain
Endometriosis	Common gynaecological condition due to presence of endometrial tissue outside the normal uterine cavity, often associated with dysmenorrhoea, dyspareunia and pelvic or lower abdominal pain
Fibromyalgia	Common syndrome associated with long-term, body-wide pain and tenderness in the joints, muscles, tendons and other soft tissues (common among women aged 20 to 50); cause: unknown
Herpes zoster infection (shingles)	Originating from inflammation after growth of herpes zoster viruses in the infected nerves
HIV related	Pain due to HIV itself, other illnesses and infections or side effects of HIV drugs; variable symptoms including peripheral neuropathy, abdominal pain, headache, joint, muscle and bone pain or herpes pain.
Inflammatory arthritis	group of chronic inflammatory rheumatic diseases including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis; progressive diseases, characterized by pain, joint destruction and decreased patient function
Intrauterine devices	Pain due to intrauterine device insertion
Irritable bowel syndrome	Chronic gastrointestinal disorder characterized by fluctuating complains of abdominal pain or discomfort and an altered bowel habit resulting in diarrhoea or constipation; pathophysiology is still unclear Often associated with depressive and anxiety disorders as well with somatic co-morbidities including fibromyalgia, chronic fatigue syndrome and chronic pelvic pain
Mixed neuropathic	Neuropathic pain from diabetic peripheral neuropathy, post-herpetic neuralgia, traumatic/surgical nerve injury, incomplete spinal cord injury, trigeminal neuralgia, multiple sclerosis or HIV-associated peripheral neuropathy
Musculoskeletal	Pain due to repetitive strain, overuse and work-related musculoskeletal disorders; injuries include a variety of disorders causing pain in bones, joints, muscles or surrounding structures; acute or chronic, focal or diffuse; includes e.g. low back pain, neck disorders, tendonitis and tendinosis, neuropathies, myalgia and stress fractures; pathophysiology not completely clear, but inflammation, fibrosis, tissue degradation, neurotransmitters and neurosensory disturbances seem to play a role
Osteoarthritis	Most common rheumatic disease; predominantly a non-inflammatory disease, but frequently treated with NSAIDs; affects the synovial joints with the hands, knees, hips and spine being the most commonly affected

Table 2

Continued

Clinical pain condition	Description
Pain-related functional GI disorders	Clinically apparent, non-organic, chronic or recurrent abdominal pain in children, with three or more episodes within 3 months that are severe enough to interfere with daily activities; attributed to several known pathophysiological determinants, including altered GI motility, enhanced visceral hypersensitivity, altered mucosal immune and inflammatory function, as well as altered central nervous or enteric nervous regulation; classified as 'somatoform disorders'
Perioperative	Pain during surgery
Phantom limb	Affects about 80% of amputees; occurs as early as within a week after amputation in 72% of patients; incidence at 6 months and 2 years not considerably different from that at onset; described as cramping, burning, tingling, sharp shooting to mixed burning–tingling or burning–cramping; aetiology not well understood; considered as neuropathic pain due to spontaneous and abnormal evoked activity in pain processing pathways.
Post-herpetic neuralgia	Pain lasting longer than 3 months after an acute herpes infection; spontaneous remission of pain unlikely.
Post-mastectomy pain	Caused by nerve damage or eventually haematoma; causes numbness, a burning pain or a dull ache; may affect the chest area as well as the armpit and arm on the operated side; varying degree of pain ranging from mild to severe
Postoperative	Pain following surgery
Postoperative cancer pain	See cancer pain
Renal colic	Common cause: passage of urinary tract calculi; sudden onset of severe pain radiating from the flank to the groin; sometimes associated with nausea, vomiting, hypertension and haematuria; origin: obstruction of urinary flow with subsequent increasing wall tension in the urinary tract; prostaglandins play an important role
Sickle cell disease	Periodic episodes of pain due to obstructed blood vessels; occurs unpredictably in any body organ or joint; frequency (1–15 periods per year), amount of pain (mild to very severe) and length of painful periods (hours to months) varies largely
Spinal cord / Nerve injury	Pain due to spinal cord or nerve injury
Temporomandibular joint disease	Disorders affecting the joint between the temporal bone on the side of the head and the mandibular (jaw) bone of the face, and the associated muscles caused by muscular hyper- or parafunction
Tension type headache	Dull, aching and non-pulsating pain affecting both sides of the head; not vascular or migrainous, not related to organic disease; most common form of headache; may be related to muscle tightening in the back of the neck and/or scalp; classified in episodic and chronic, differentiated by frequency and severity of symptoms
Trauma	Pain due to physical trauma, e.g. burn injuries
Trigeminal neuralgia	Chronic syndrome of neuropathic pain affecting the facial area; severe pain affecting even simple physiological functions, such as chewing, swallowing, tooth brushing, washing, touching the face, etc.; pathophysiology unclear, probably induced by compression of the trigeminal nerve at its origin by the brain stem, blood vessels or a tumour; local pressure causes demyelination resulting in abnormal depolarization and ectopic pulses

efficacy in these 35 pain conditions, the search was narrowed by adding the keyword 'analgesia', which yielded 126 hits. In addition to the aforementioned analgesics and co-analgesics, benzodiazepines and clonidine were also identified. While not belonging to a particular class of analgesic, these substances have been assessed for their analgesic efficacy in both clinical and experimental settings.

In the *Cochrane* reviews, analgesic efficacy was assessed based on primary outcomes such as changes in pain intensity by at least 50 %; ratings of pain intensity were obtained from visual analogue or categorical scales, or third-party pain scoring. Secondary outcomes were opioid dosing requirements for breakthrough analgesia, time elapsed until administration of rescue analgesics, opioid-sparing effects of non-opioid drugs, patients' preference, therapy withdrawals due to adverse events or lack of efficacy. The 126 hits were classified into positive (+) or negative (–) evidence for analgesic efficacy, separately for drugs or drug classes (Table 3). If the *Cochrane* review stated that the available evidence did not allow a final conclusion to be reached, the study was rated as neither positive nor negative (±).

Evidence for clinical efficacy of analgesic drug classes. The findings of positive, negative or undefinable evidence with respect to the analgesic efficacy of drugs or drug classes in the 35 clinical pain settings addressed in the *Cochrane* reviews are summarized in Table 3. As opioids have been used as analgesics for thousands years, their effects in a large number of

Table 3

Efficacy of analgesics and co-analgesics in clinical pain conditions according to the systematic reviews published in *The Cochrane Library*

Pain condition	Opioids		Non-opioid analgesics									Co-analgesics					Others		References
	Opioids strong	Opioids weak	NSAIDs	Dipyrone	Paracetamol	COX-2 inhibitors	Flupirtine	Capsaicin	AZD-1386	Ketamine	Cannabinoids	Carbamazepine	Pregabalin	Gabapentin	Lamotrigin	Antidepressants	Benzodiazepines	Clonidine	
Abdominal pain	1																		(Manterola *et al.*, 2011)
Acute migraine			1	1			±1												(Million *et al.*, 1984; Ramacciotti *et al.*, 2007; Rabbie *et al.*, 2010)
Atypical facial pain																1			(Saarto and Wiffen, 2007)
Burn injury	1																		(Quigley, 2002)
Burning mouth syndrome																–1			(Saarto and Wiffen, 2007)
Cancer	1		1				±1			±1									(Scheef, 1987; Luben *et al.*, 1994; Quigley, 2002; Bell *et al.*, 2003; Ballantyne and Carwood, 2005; McNicol *et al.*, 2005; Zeppetella and Ribeiro, 2006; Nicholson, 2007; Wiffen and McQuay, 2007)
Central neuropathic										±1		1	1		–1	±1			(Fisher *et al.*, 2000; Saarto and Wiffen, 2007; Moore *et al.*, 2009j; Wiffen *et al.*, 2011a,b)
Chemotherapy induced															–1	1			(Saarto and Wiffen, 2007; Wiffen *et al.*, 2011a)
Child birth/labour	1	1	1																(Elbourne and Wiseman, 2000; Hedayati *et al.*, 2003; Ullman *et al.*, 2010; Deussen *et al.*, 2011;)
Diabetic neuropathy (PDN)								±1				1	1	1	–1	1			(Derry *et al.*, 2009d; Moore *et al.*, 2009j; 2011; Saarto and Wiffen, 2007; Wiffen *et al.*, 2011a,b)
Dysmenorrhoea			1																(Marjoribanks *et al.*, 2010)
Endometriosis			±1																(Allen *et al.*, 2009a)
Fibromyalgia							±1			±1			1	1		1	–1		(Worz, 1991; Fisher *et al.*, 2000; Lunn *et al.*, 2009; Moore *et al.*, 2009j; 2011; Corrigan *et al.*, 2012; Tort *et al.*, 2012)
Herpes zoster infection												–1							(Wiffen *et al.*, 2011b)
HIV related								±1							–1	–1			(Saarto and Wiffen, 2007; Derry *et al.*, 2009d; Wiffen *et al.*, 2011a)
Inflammatory arthritis*	±1	–1	±1		±1			±1			±1					±1	–1		(Suarez-Almazor *et al.*, 2000; Gotzsche and Johansen, 2004; Ramiro *et al.*, 2011; Richards *et al.*, 2011; 2012a,b; Whittle *et al.*, 2011; Wienecke and Gotzsche, 2004)
Intrauterine devices			–1																(Allen *et al.*, 2009b)

Table 3

Continued

Pain condition	Opioids: Opioids strong	Opioids: Opioids weak	Non-opioid analgesics: NSAIDs	Non-opioid analgesics: Dipyrone	Non-opioid analgesics: Paracetamol	Non-opioid analgesics: COX-2 inhibitors	Non-opioid analgesics: Flupirtine	Non-opioid analgesics: Capsaicin	Non-opioid analgesics: AZD-1386	Non-opioid analgesics: Ketamine	Non-opioid analgesics: Cannabinoids	Co-analgesics: Carbamazepine	Co-analgesics: Pregabalin	Co-analgesics: Gabapentin	Co-analgesics: Lamotrigin	Co-analgesics: Antidepressants	Others: Benzodiazepines	Others: Clonidine	References
Irritable bowel syndrome																1			(Ruepert *et al.*, 2011)
Mixed neuropathic	1	1												1	−1				(Duhmke *et al.*, 2004; Eisenberg *et al.*, 2006; Noble *et al.*, 2010; Moore *et al.*, 2011; Wiffen *et al.*, 2011a)
Musculoskeletal	1	1	1				1									−1			(Green *et al.*, 2002; Deshpande *et al.*, 2007; Roelofs *et al.*, 2008; Urquhart *et al.*, 2008; Massey *et al.*, 2010; Noble *et al.*, 2010; Ueberall *et al.*, 2011)
Osteoarthritis	1	1	±1		1	1													(Towheed *et al.*, 2000; 2006; Watson *et al.*, 2000; Garner *et al.*, 2005; Cepeda *et al.*, 2006; Nuesch *et al.*, 2009; Noble *et al.*, 2010)
Pain-related functional GI disorders																−1			(Kaminski *et al.*, 2011)
Perioperative			1																(Standing *et al.*, 2009; Ahmad *et al.*, 2010)
Phantom limb	1									1				1		−1			(Fisher *et al.*, 2000; Alviar *et al.*, 2011; Moore *et al.*, 2011)
Post-herpetic neuralgia								±1		±1		1	1	1		1			(Fisher *et al.*, 2000; Saarto and Wiffen, 2007; Derry *et al.*, 2009d; Moore *et al.*, 2009j; 2011; Wiffen *et al.*, 2011b)
Post-mastectomy pain								±1											(Derry *et al.*, 2009d)
Postoperative	1	1	1	1	1	1				1			−1	1					(Schmid *et al.*, 1999; Collins *et al.*, 2000a,b; Edwards *et al.*, 2000a,b,c,d;2010; Moore *et al.*, 2000; Quigley, 2002; Mason *et al.*, 2004; Werawatganon and Charuluxanun, 2005; Bell *et al.*, 2006; Weil *et al.*, 2007; Toms *et al.*, 2008; 2009; Barden *et al.*, 2009; Bulley *et al.*, 2009; Gaskell *et al.*, 2009; Hall *et al.*, 2009; Lloyd *et al.*, 2009; Moore *et al.*, 2009a,b,c,d,e,f,g,h,i,j; Sultan *et al.*, 2009; Tirunagari *et al.*, 2009; Derry *et al.*, 2009a,b,c; 2010; Roy *et al.*, 2010; Straube *et al.*, 2010; Wasey *et al.*, 2010; Moll *et al.*, 2011; Traa *et al.*, 2011; Tzortzopoulou *et al.*, 2011; Zhang *et al.*, 2011; Clarke *et al.*, 2012; Derry and Moore, 2012)

Table 3

Continued

Pain condition	Opioids: Opioids strong	Opioids: Opioids weak	Non-opioid analgesics: NSAIDs	Non-opioid analgesics: Dipyrone	Non-opioid analgesics: Paracetamol	Non-opioid analgesics: COX-2 inhibitors	Non-opioid analgesics: Flupirtine	Non-opioid analgesics: Capsaicin	Non-opioid analgesics: AZD-1386	Non-opioid analgesics: Ketamine	Non-opioid analgesics: Cannabinoids	Co-analgesics: Carbamazepine	Co-analgesics: Pregabalin	Co-analgesics: Gabapentin	Co-analgesics: Lamotrigin	Co-analgesics: Antidepressants	Others: Benzodiazepines	Others: Clonidine	References
Postsurgical cancer pain	1							±1											(Quigley, 2002; Derry *et al.*, 2009d)
Renal colic	1		1	±1															(Edwards *et al.*, 2002; Holdgate and Pollock, 2005; Quigley, 2002)
Sickle cell disease	±1																		(Dunlop and Bennett, 2006)
Spinal cord / Nerve injury										±1				1	–1	–1			(Fisher *et al.*, 2000; Saarto and Wiffen, 2007; Moore *et al.*, 2011; Wiffen *et al.*, 2011a)
Temporomandibular joint disease			1			–1		–1						–1				–1	(Mujakperuo *et al.*, 2010)
Tension-type headache				1			±1												(Worz, 1991; Worz *et al.*, 1995; Ramacciotti *et al.*, 2007)
Trauma	1																		(Quigley, 2002)
Trigeminal neuralgia	1											1		1	–1				(Noble *et al.*, 2010; Moore *et al.*, 2011; Wiffen *et al.*, 2011a,b)
No. of clinical pain conditions showing positive evidence for analgesia	13	5	9	3	2	2	1	0	0	2	0	4	4	8	0	6	0	0	
No. of clinical pain conditions showing negative evidence for analgesia	0	1	1	0	0	1	0	1	0	0	0	1	1	1	7	6	3	0	
No. of clinical pain conditions showing mixed evidence for analgesia	2	0	3	1	1	0	4	6	0	5	1	0	0	0	0	2	0	0	

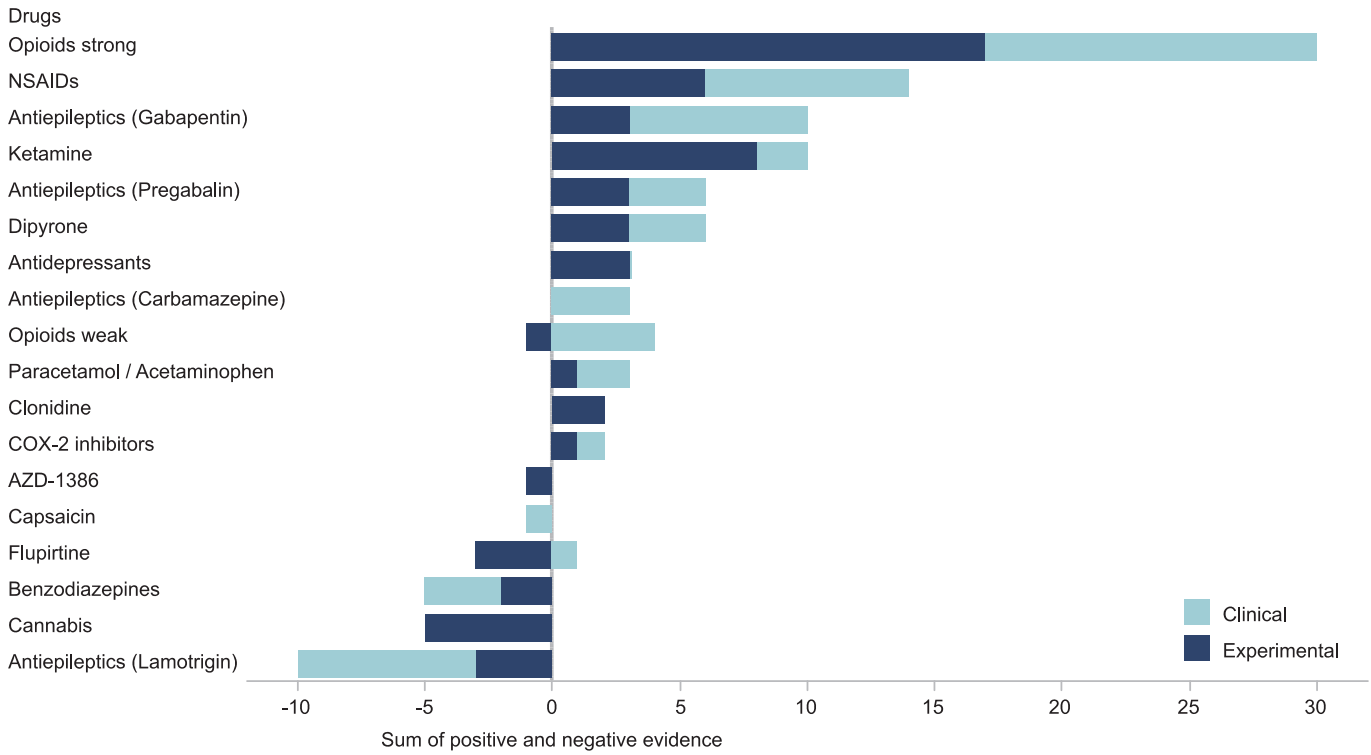

Figure 1

Drug class and sum of successful and unsuccessful applications in clinical pain conditions (max. number possible: 35) and experimental pain models (max. number possible: 33). The graphs suggest a correlation between positive and negative outcomes in clinical and experimental pain conditions. This correlation was indeed present as indicated by a Spearman's σ of 0.71 ($P < 0.001$).

clinical pain settings were analyzed in the *Cochrane* reviews ($n = 15$ clinical pain conditions). From the results, opioids are ineffective in inflammatory arthritis, which is consistent with their lack of anti-inflammatory effects but does not accord with results showing the presence of peripheral opioid effects in inflammatory environments (Stein *et al.*, 1989; 1990). Antidepressants were also thoroughly assessed for their effects in different ($n = 14$) pain settings. According to the results, when used as co-analgesic, they are effective in several types of neuropathic pain but fail, for example, in phantom limb pain. NSAIDs have been reviewed for $n = 13$ clinical pain settings. Surprisingly, an efficacy of NSAIDs in inflammatory arthritis does not unequivocally emerge from the present evidence. Similarly, the unexpected finding that patients chronically treated with NSAIDs experienced more pain was hypothesized to be caused by the suppression of anti-inflammatory lipid mediators as a consequence of chronic COX inhibition (Lotsch *et al.*, 2010). When the data were sorted for the sum of positive and negative evidence (Figure 1; undecided outcomes were considered the same as no evidence) for analgesic efficacy, the order was opioids (+13/–0/ ± 2), NSAIDs (+9/–1/ ± 3) and gabapentin (+8/–1/ ± 0). The drug with most negative evidence (analgesic inefficacy) was lamotrigin (+0/–7/ ± 0).

Efficacy of analgesics on experimental pain

Experimental human pain models. As pain is a subjective perception, it cannot be measured but is communicated by the subject (McCaffery and Moss, 1967). The development of human pain models was a consequence of the quantification of pain by using objective measures to reflect subjective responses (Beecher, 1959). However, the fundamental limitation applies; the data recorded are not pain itself but a psychophysical or bioresponse to nociceptive stimulation (Handwerker and Kobal, 1993). The major components of pain models are (i) the nociceptive stimuli occasionally combined with tissue priming such as intentional local inflammation and (ii) the readouts of the responses to these stimuli. For ethical reasons, human pain models are more limited in these components than animal models and still largely follow the criteria defined in 1956 by Beecher (1956) to quantify analgesic drug effects; these include minimal tissue damage, correlation between stimulus strength and pain intensity, stability over time and sensitivity (Gracely and Melzack, 1989). Several types of pain stimuli have been established and are classified according to their physical properties into electrical, thermal (contact or laser heat, contact or immersion cold), mechanical (blunt or punctate pressure), ischaemic and chemical pain stimuli. Established psychophysical readouts include visual analogue and numerical rating scales or dichotomous measures such as pain threshold (i.e. the stimulus strength at which the evoked sensation changes from mere perception to mild pain) and pain tolerance (i.e. the stimulus strength at which pain becomes unbearable). It should be noted that most of these pain measurements are obtained from the quantification of the physical strength of

nociceptive stimuli associated with certain perceptional changes.

Apart from psychophysiological measures, human pain sensation is accessible by several electrophysiological measurements. The negative-mucosa potential (NMP) represents the sum of generator potentials of trigeminal receptor neurons in response to nociceptive stimulation (Kobal, 1985). NMPs have been used to separate peripheral from central components of the analgesic action of NSAIDs (Lötsch *et al*., 1997). In contrast, the EEG-derived pain-related potentials (ERP) are direct correlates of neuronal activation following chemosensory, electrical or laser heat stimulation and allow for the investigation of the central processing of painful information, which is thought to depend less on the subject's response bias than psychophysiological measures (Hummel *et al*., 1994; Thürauf *et al*., 1994). Finally, magnetencephalography (Huttunen *et al*., 1986) and functional magnetic resonance imaging has opened up the field of imaging to study the human nociceptive system in detail (Tracey, 2001), including the identification of different effects of analgesics (Oertel *et al*., 2008b).

Search strategy. For all the analgesics for which the Cochrane library provided evidence of efficacy in clinical pain, their efficacy in human experimental pain models was searched in two comprehensive recent reviews (Staahl *et al*., 2009a,b) and supplemented by a PubMed search for 'experimental pain + human + randomized' with the extension of the keywords (Table 1) 'opioid', 'NSAID', 'dipyrone', 'paracetamol OR acetaminophen', 'coxib*', 'flupirtine', 'nefopam', 'capsaicin OR TRPV1', 'cannabinnoids OR THC', 'anticonvulsant', 'antidepressant', 'ketamin* OR NMDA' and additionally 'benzodiazepin OR *zepam*' and 'clonidine'. Furthermore, the TRPV1 antagonist AZD-1386 was included as an example of a newly developed analgesic (Table 1). This search identified 33 different setups of experimental pain models (Table 4). A study was classified as reporting positive (+) evidence if a drug produced analgesia in an experimental pain model indicated by a statistically significant reduction in pain intensity, an increase in pain threshold or tolerance, a decrease in area of hyperalgesia or a decrease in the amplitudes of pain-related evoked potentials. Since the information available on drug-induced analgesia in experimental pain models did not fulfil the Cochrane criteria and was based on published results from single experiments, evidence was only rated as positive if all major readouts of a specific test indicated analgesia. Negative (–) evidence was treated similarly. Some studies failed to provide clear results and were rated as neither positive nor negative (±, Table 5).

Evidence for clinical efficacy of analgesic drug classes. Table 5 lists the positive, negative and indefinable evidence for all analgesics in the experimental pain conditions identified. Based on these criteria, the effects of opioids were assessed in the greatest number of experimental pain models (n = 22), followed by NSAIDs (n = 19) and NMDA receptor antagonists (n = 15). When sorted for cumulative positive or negative evidence (undefined results were regarded as no evidence) of analgesic efficacy (Figure 1), the drug order in the experimental models agreed with that observed in clinical pain. Opioids (+18/–1/±3 positive, negative and undecided outcomes, respectively) were the most effective analgesics, followed by NSAIDs (+9/–3/±7) and, in contrast to the clinical studies, ketamine (+8/–0/±7). The drug class with most negative evidence was cannabinoids (+1/–6/±2). Despite their approval for neuropathic pain associated with multiple sclerosis, cannabinoids were rarely demonstrated to provide analgesia and sometimes increased experimental pain (Kraft *et al*., 2008).

Agreement and non-agreement between experimental and clinical analgesia

A hypothesis pursued in this review was that when a drug is effective in both an experimental pain model and a clinical setting, then the experimental model may predict the efficacy of further drugs in this particular clinical setting. The overall agreement between outcomes in experimental and clinical assessments (Figure 1) suggested a correlation between the results of both approaches, which was statistically significant (sum of positive and negative evidence of drug efficacy in either clinical or experimental settings, respectively: Spearman's ρ: = 0.71, $P < 0.001$). However, contradictory results were observed, for example, weak opioids shown to be effective in five of six clinical pain conditions were more rarely shown to be effective in experimental studies.

However, a general correlation between the positive and negative findings in experimental and clinical pain assessments does not provide the necessary basis for selecting pain models to develop analgesics for particular clinical pain settings. Identification of the pain model or set of models best suited for this purpose requires more detailed information about which experimental models identified analgesics that were also effective in the clinical pain setting (Figure 2). Most agreements, however, were based on single reports. The validity of predicting the efficacy of a drug on a particular clinical pain condition from its effects in a particular experimental pain model increases with an increase in the number of different drugs for which results in experimental and clinical assessments agreed. On this basis, the largest selection of experimental pain models exists for postoperative pain. Agreement across several drug classes was found for (i) UV-B induced hyperalgesia combined with punctate pressure, which predicted analgesia for five drugs (i.e. strong opioids, NSAIDs, paracetamol, COX-2 inhibitors and gabapentin) (Figure 2). In decreasing order, further agreement for postoperative pain was found in (ii) UV-B induced hyperalgesia combined with contact heat stimuli (four drugs: strong opioids, NSAIDs, paracetamol and gabapentin), (iii) blunt pressure (strong opioids, NSAIDs and dipyrone), (iv) electrical hyperalgesia plus punctate pressure (strong opioids, paracetamol and gabapentin) and (v) chemical hyperalgesia with or (vi) without punctate pressure (both models: strong opioids, NSAIDs and gabapentin). Other clinical pain conditions in which analgesia was correctly predicted by a pain model for at least three drugs included mixed neuropathic pain, which was predicted by chemical hyperalgesia in combination with punctate pressure for strong opioids, gabapentin and lamotrigin, whereas lamotrigin was correctly predicted to be ineffective. Note that 'correct' is being used for the prediction of

Table 4

Experimental pain models that are frequently used according to the literature (Staahl *et al.*, 2009a,b) and PubMed

Experimental pain condition	Experimental stimulus/model	Stimulation site
Chemical (punctate, nasal)	Gaseous CO_2 stimulus	Nasal mucosa
Chemical hyperalgesia	Capsaicin	Skin (topical, intracutaneous)
	Hypertonic saline	Skin (intracutaneous), intramuscular
Chemical hyperalgesia (visceral)	Hydrochloric acid	Gastrointestinal tract (oesophagus, gut)
Chemical hyperalgesia + Cold (contact)	Menthol + Medoc-TSA (cold)	Skin (topical)
Chemical hyperalgesia + Heat (contact)	Capsaicin + Medoc-TSA (heat)	Skin (topical, intracutaneous)
Chemical hyperalgesia + Pressure (blunt)	Glutamate injection + Algometry	Intramuscular injection (masseter, splenius)
Chemical hyperalgesia + Pressure (punctate)	Capsaicin + von Frey	Skin (topical, intracutaneous)
	Capsaicin + Pinprick	Skin (topical, intracutaneous)
	Hypertonic saline + Pinprick	Intracutaneous, Intramuscular injection (masseter, splenius)
Cold thermode (contact)	Medoc-TSA (cold)	Skin
Cold water (contact)	Ice Water	Skin
Electrical hyperalgesia + Pressure (punctate)	Neurometer + Pinprick	Skin (topical, intracutaneous), dental pulp, earlobe, intramuscular (muscle RIII)
Electricity	Neurometer	Skin (topical, intracutaneous), dental pulp, earlobe, intramuscular
Heat (contact)	Medoc-TSA (heat)	Skin (topical)
Heat (punctate)	Laser	Skin (topical)
Heat (visceral)	Balloon heat	Gastrointestinal tract (oesophagus, gut)
Inflammatory hyperalgesia	Freeze lesion	Skin (topical)
Inflammatory hyperalgesia (punctate, nasal)	Dry air	Nasal mucosa
Inflammatory hyperalgesia + Electricity	Freeze lesion + Electrical stimulus	Skin (topical)
Inflammatory hyperalgesia + Heat (contact)	Freeze lesion + Medoc-TSA (Heat)	Skin (topical)
Inflammatory hyperalgesia + Pressure (punctate)	Freeze lesion + Pinprick	Skin (topical)
Ischaemic pain	Tourniquet	Arm, forearm, thigh, calf, finger, toe, etc.
Mechanical hyperalgesia + Pressure (punctate)	Repeated Pinprick	Skin (topical)
Muscle ache	Delayed onset muscle soreness	Jaw muscle
Pressure (blunt)	Algometry	Interdigital web, phalanx, finger pulp, extensor digitor
Pressure (punctate)	Pinprick	Skin (topical)
Pressure (visceral)	Balloon distension	Gastrointestinal tract (oesophagus, gut)
Thermal hyperalgesia	Heat lesion	Skin (topical)
Thermal hyperalgesia + Heat (contact)	Heat lesion + Medoc-TSA (heat)	Skin (topical)
Thermal hyperalgesia + Pressure (punctate)	Heat lesion + Pinprick	Skin (topical)
UV-B hyperalgesia + Heat (contact)	UV-B radiation + Medoc-TSA (Heat)	Skin (topical)
UV-B hyperalgesia + Pressure (punctate)	UV-B radiation + Pinprick	Skin (topical)

the drug's efficacy on clinical pain by the drug's efficacy on experimental pain, deduced for clinical settings and experimental models. Thus, from the evidence available, five clinical pain conditions were correctly predicted by seven different pain models for at least three different drugs. Most of these models combine a sensitization method with an acute pain stimulus (e.g. UV-B or capsaicin).

However, several unsuitable pain models were also used to predict efficacy in certain clinical conditions (Figure 3). Analgesia in diabetic neuropathic pain, mixed neuropathic pain, pain due to spinal cord or nerve injury and trigeminal neuralgia was incorrectly predicted by the cold water immersion test. In this model, lamotrigin was ineffective, whereas gabapentin provided analgesia; however, clinically the opposite was observed. Several more failures of experimental models to predict analgesia in particular clinical settings were also identified (Figure 3).

Table 5

Efficacy of analgesics and co-analgesics in experimental pain settings

Experimental stimulus/model	Opioids		Non-opioid analgesics								Co-analgesics					Others		References
	Opioids strong	Opioids weak	NSAIDs	Dipyrone	Paracetamol	COX-2 inhibitors	Flupirtine	Capsaicin	AZD-1386	Ketamine	Cannabinoids	Carbamazepine	Pregabalin	Gabapentin	Lamotrigin	Antidepressants	Benzodiazepines	Clonidine	
Gaseous CO_2 stimulus	1	±1	±1	1	±1		1				–1				–1	1	–1		(Kobal and Raab, 1986; Hummel *et al.*, 1991; Thurauf *et al.*, 1994; Staahl *et al.*, 2009a,b;)
Capsaicin			±1				–1			±1	±1			1				1	(Eisenach *et al.*, 2000; Klein *et al.*, 2008; Wang *et al.*, 2008; Staahl *et al.*, 2009a,b)
Hypertonic saline	4		2		–1									±1					(Svensson *et al.*, 2003; Staahl *et al.*, 2009a,b)
Hydrochloric acid									–1	1									(Staahl *et al.*, 2009a,b; Krarup *et al.*, 2011)
Menthol + Medoc-TSA (cold)		1	–1										1						(Altis *et al.*, 2009; Staahl *et al.*, 2009a,b)
Capsaicin + Medoc-TSA (heat)	–1		1							±1				1					(Staahl *et al.*, 2009a,b; Andresen *et al.*, 2011)
Glutamate injection + Algometry										2									(Staahl *et al.*, 2009a,b; Alstergren *et al.*, 2010)
Capsaicin + von Frey													1						(Wang *et al.*, 2008; Staahl *et al.*, 2009a,b)
Capsaicin + Pinprick	4		1				–1			±1	–1			3	–2				(Klein *et al.*, 2008; Staahl *et al.*, 2009a,b; Andresen *et al.*, 2011)
Hypertonic saline + Pinprick														–1					(Staahl *et al.*, 2009a,b)
Medoc-TSA (cold)	±1									±1	–1				–1				(Staahl *et al.*, 2009a,b)
Ice Water	9	±1	±1		2						–2			–1	1	±1			(Staahl *et al.*, 2009a,b)
Neurometer + Pinprick	6	±1			3	±1								1					(Koppert *et al.*, 2004; Filitz *et al.*, 2008; Staahl *et al.*, 2009a,b)
Neurometer	20	±1	±1	1	±1		–1			3	±1		1	±1		3			(Kobal and Raab, 1986; Rohdewald *et al.*, 1988; Quante *et al.*, 2004; Filitz *et al.*, 2008; Staahl *et al.*, 2009a,b; Olesen *et al.*, 2011)
Medoc-TSA (heat)	22	±1							1	±1	–3			–1	–2	1		1	(Eisenach *et al.*, 2000; Staahl *et al.*, 2009a,b; Ing Lorenzini *et al.*, 2011; Krarup *et al.*, 2011)
Laser	1		1		±1					±1						–1			(Staahl *et al.*, 2009a,b)
Balloon heat	±1								1										(Arendt-Nielsen *et al.*, 2009; Staahl *et al.*, 2009a,b)
Freeze lesion			1																(Staahl *et al.*, 2009a,b)
Dry air			±1																(Staahl *et al.*, 2009a,b)
Freeze lesion + Electrical stimulus	1																		(Staahl *et al.*, 2009a,b)
Freeze lesion + Medoc-TSA (heat)			1																(Staahl *et al.*, 2009a,b)

Table 5

Continued

Experimental stimulus/model	Opioids		Non-opioid analgesics									Co-analgesics					Others		References
	Opioids strong	Opioids weak	NSAIDs	Dipyrone	Paracetamol	COX-2 inhibitors	Flupirtine	Capsaicin	AZD-1386	Ketamine	Cannabinoids	Carbamazepine	Pregabalin	Gabapentin	Lamotrigin	Antidepressants	Benzodiazepines	Clonidine	
Freeze lesion + Pinprick	2				–1														(Staahl *et al.*, 2009a,b)
Tourniquet	±1	–1	–1							1							–1		(Posner, 1984; Staahl *et al.*, 2009a,b)
Repeated Pinprick	3																		(Staahl *et al.*, 2009a,b)
Delayed onset muscle soreness		–1	±1																(Bajaj *et al.*, 2003; Staahl *et al.*, 2009a,b)
Algometry	11	±1	6	1	–3				–1	2	–1					2			(Forster *et al.*, 1992; Staahl *et al.*, 2009a,b; Krarup *et al.*, 2011)
Pinprick	1		±1				–1			±1	1			±1		–1			(Klein *et al.*, 2008; Staahl *et al.*, 2009a,b)
Balloon distension	2								–1	1						1			(Arendt-Nielsen *et al.*, 2009; Staahl *et al.*, 2009a,b; Krarup *et al.*, 2011)
Heat lesion			–1																(Staahl *et al.*, 2009a,b)
Heat lesion + Medoc-TSA (heat)	2									2									(Staahl *et al.*, 2009a,b)
Heat lesion + Pinprick	6									2									(Staahl *et al.*, 2009a,b)
UV-B radiation + Medoc-TSA (Heat)	1		3		1									1					(Staahl *et al.*, 2009a,b; Ing Lorenzini *et al.*, 2011)
UV-B radiation + Pinprick	2		2		1	1								1					(Maihofner *et al.*, 2007; Staahl *et al.*, 2009a,b; Andresen *et al.*, 2011; Ing Lorenzini *et al.*, 2011)
No. of experimental models showing positive evidence for analgesia	**18**	**1**	**9**	**3**	**4**	**1**	**1**	**0**	**2**	**8**	**1**	**0**	**3**	**6**	**1**	**5**	**0**	**2**	
No. of experimental models showing negative evidence for analgesia	**1**	**2**	**3**	**0**	**3**	**0**	**4**	**0**	**3**	**0**	**6**	**0**	**0**	**3**	**4**	**2**	**2**	**0**	
No. of experimental models showing mixed evidence for analgesia	**3**	**6**	**7**	**0**	**3**	**1**	**0**	**0**	**0**	**7**	**2**	**0**	**0**	**3**	**0**	**1**	**0**	**0**	

The table presents positive evidence (green, +), negative evidence (red, –), mixed evidence (orange, ±) for analgesic drug effects in the respective pain model. Evidence was only rated as positive if all major readouts of a specific test, e.g. increase in pain threshold or tolerance, a decrease in area of hyperalgesia or a decrease in amplitudes of pain-related evoked potentials, presented in a publication indicated analgesia. The same was true for negative evidence. Studies providing mixed results, e.g. due to inconsistent readouts, were rated as neither positive nor negative. Attached numbers represent available publications providing positive, negative or mixed evidence. However, since a weighting was presently unwanted, the number of publications was subsequently ignored; that is, although 20 publications showed that opioids were effective analgesics during electrical stimulation but only once during laser stimulation, both experimental models were subsequently treated equally as being once successful in showing the analgesic effectiveness of opioids.

Figure 2

Clinical pain conditions for which analgesia or no analgesia was correctly predicted by an experimental pain condition. The table presents all combinations of experimental pain models and clinical pain conditions in which analgesics were effective or ineffective in both, the clinical and the experimental pain condition (correct prediction of clinical effectiveness by an experiment). The size of the pie charts correlates with the number of drugs that were correctly predicted. The colours of the segments indicate the drug or drug class that was correctly predicted.

Future directions

Human experimental pain models implement psychosocial and social–cultural factors and avoid pharmacologically relevant species differences, for example, rats cannot produce the active 6-glucuronide of morphine (Oguri *et al.*, 1990), and dogs, guinea pigs and rats can invert *R*-flurbiprofen to the COX-2 inhibiting *S*-enantiomer (Menzel-Soglowek *et al.*, 1992). However, ethical considerations restrict invasive models to small skin (Schmidtko *et al.*, 2007) and mucosal tissue probes. This suggests a complementary use of human and animal models in the translational development of analgesic drugs, as established more than half a century ago when Beecher's criteria for experimental pain stimuli included applicability in both humans and animals (Beecher, 1956). However, the future scientific focus is not on cross-validation of human with animal pain models but on cross-validation of human experimental models with clinical pain. To fully reveal their potential as a cost-saving tool in analgesic drug development placed between basic science and clinical assessments, human pain models need to be validated with clinical pain in future studies. Some biases unequivocally resulting from the selection of pain models in the studies presently analysed also need to be eliminated, which might slightly shift the present picture of predictivity towards different models. Future analyses will include combinations of models as suggested from the present results where a combined pain model had the best evidence for prediction of a particular clinical pain setting (Figure 2). Considering the complexity of the pain phenotype, contemporary informatics tools are an indispensable part of these approaches. Initial attempts have clustered quantitative sensory testing results to obtain more homogeneous groups of neuropathic pain patients to define individual treatments (Baron *et al.*, 2010). Thus, identifying combinations of experimental models and clinical validation seems to be the direction for the development of experimental pain models toward predictive tools in drug development.

Concluding remarks

A variety of different experimental pain models allow pain and analgesia in humans to be studied under controlled laboratory conditions. While the perceived prediction of clinical pain by human models seems to be no better than that obtained with animal models, where the incomplete translation has caused disappointment (Mogil, 2009), the present analysis showed a considerable agreement between the results obtained with human pain models and the clinical efficacy of analgesics. This supports expectations that human

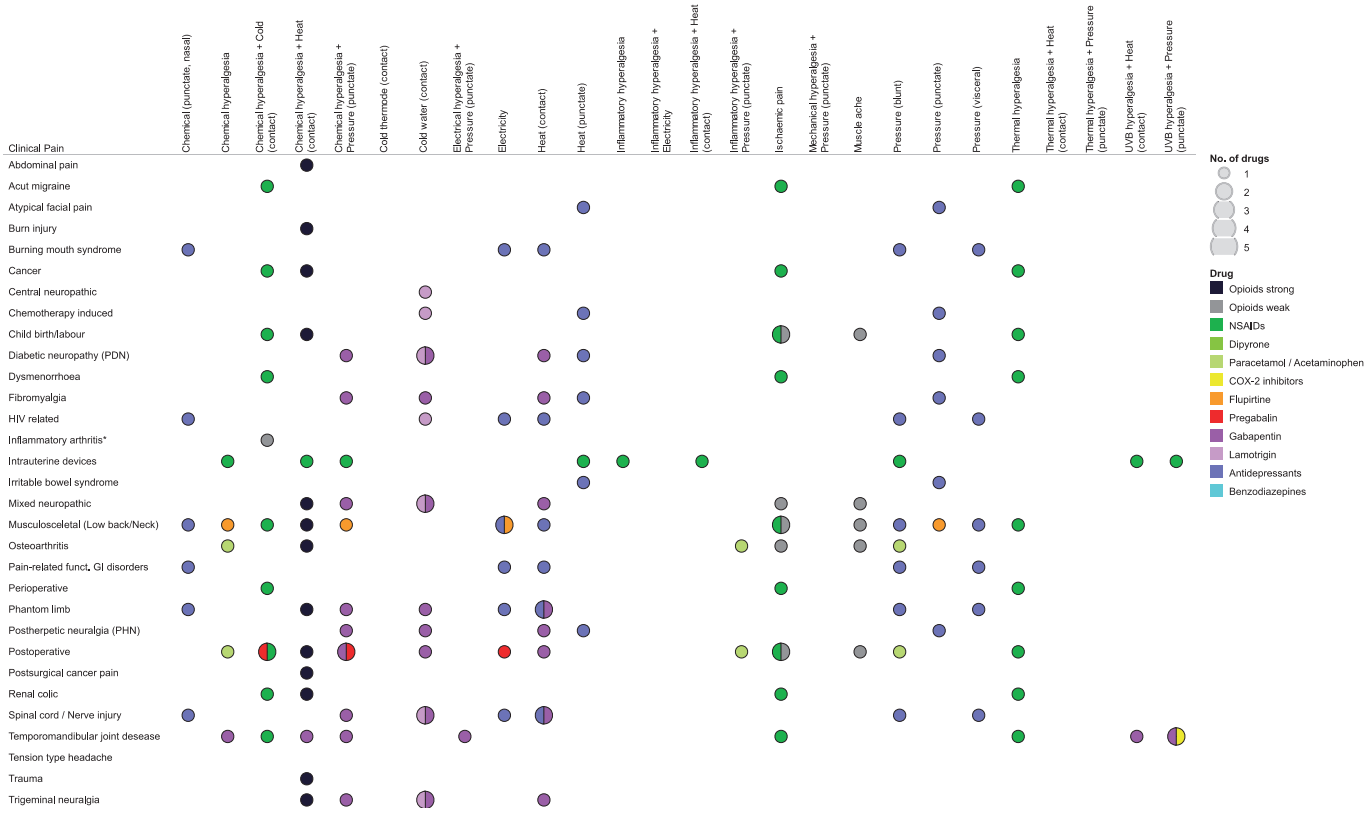

Figure 3

Clinical pain conditions for which analgesia or no analgesia was incorrectly predicted by an experimental pain condition. The table presents all combinations of experimental pain models and clinical pain conditions in which analgesics were effective in only one condition, e.g. the clinical pain condition, while being ineffective in the other, e.g. experimental pain condition (incorrect prediction of clinical effectiveness by an experiment). The size of the pie charts correlates with the number of drugs that were incorrectly predicted. The colour of the segments indicates the drug or drug class that was correctly predicted.

experimental models can be developed into truly predictive tools saving costs for analgesic drug development, and provide expert knowledge about (i) the pharmacological actions of analgesic drugs, (ii) physiological bases of the experimental pain models and (iii) the pathophysiology and pathopsychology of clinical pain. Clinical phase II studies will not be completely replaced by experimental studies, yet their number may be reduced due to a focused pre-selection that can be obtained with experimental studies, as outlined here. The presently identified agreements and non-agreements between analgesic effects on experimental and on clinical pain may serve as a basis to identify human pain models that bridge basic science with clinical pain research.

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Conflict of interest

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