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Opinion

Drug Repurposing for the Development of Novel Analgesics

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Drug development consumes huge amounts of time and money and the search for novel analgesics, which are urgently required, is particularly difficult, having resulted in many setbacks in the past. Drug repurposing – the identification of new uses for existing drugs – is an alternative approach, which bypasses most of the time- and cost-consuming components of drug development. Recent, unexpected findings suggest a role for several existing drugs, such as minocycline, ceftriaxone, sivelestat, and pioglitazone, as novel analgesics in chronic and neuropathic pain states. Here, we discuss these findings as well as their proposed antihyperalgesic mechanisms and outline the merits of pathway-based repurposing screens, in combination with bioinformatics and novel cellular reprogramming techniques, for the identification of novel analgesics.

The Search for Novel Analgesics

While a significant proportion of pain patients adequately respond to analgesics such as opioids or nonsteroidal anti-inflammatory drugs, some do not and many patients who do respond suffer from major adverse effects [1–3]. Thus, there is an emerging need for analgesics that are both effective and safe. However, despite huge investment by the pharmaceutical industry, a variety of setbacks in target-based development of novel analgesics, as well as difficulties in translating promising preclinical data to outcomes in patients, have led many big pharmaceutical companies to leave the field of novel analgesic development [4]. Thus, the lack of novel blockbuster treatments, apparent in a number of disease indications, is also apparent in the pain field [5].

Despite the existence of many potential targets, translation to the clinic of antinociceptive compounds, identified through target-based discovery, continues to be hampered by the lack of both predictive animal and human models, although use of multiple assessments may offer a way forward [6,7]. Even promising target receptors or ion channels, such as the transient receptor potential vanilloid subtype ion channel TRPV1, which have been functionally linked to many pathophysiological pain states in preclinical studies [8,9], are difficult to target. Despite the widespread clinical use and success of the TRPV1 agonist capsaicin, for instance, in the local treatment of postherpetic neuralgia, a selective and safe TRPV1 antagonist for clinical use is still unavailable. Systemic inhibition of TRPV1 caused hyperthermia in human volunteers in early phase clinical trials by inhibiting a central nervous system (CNS) subpopulation of TRPV1 [10,11] and the important and often broad physiological functions of these proteins confound approaches to systemic inhibition. This is reflected in the fact that now, 18 years after the first functional description of TRPV1 in the nociceptive system [12], still no TRPV1 antagonist is clinically available.

Trends

The search for novel analgesics is particularly arduous and has encountered many setbacks in the past. In Phase II clinical studies, approximately 50–60% of potential substances fail because of lack of efficacy and a further 25% because of safety issues.

Drug repurposing represents an alternative to time- and money-intensive *de novo* drug development, because a repurposed drug can be considered safe in the clinical setting.

Recent findings suggest the potential for several widely used drugs to be employed as novel analgesics, among them, antibiotics, antidiabetic compounds, and phosphodiesterase inhibitors.

Pathway-based repurposing screens may identify more drugs with analgesic properties that may be repurposed as novel analgesics.

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Apart from TRPV1, findings from preclinical studies targeting the neurokinin-1 receptor or the fatty acid amide hydrolase FAAH1 could not be translated to humans and substances modulating these proteins failed in clinical trials [13,14]. These difficulties in translating preclinical effects not only reflect limitations in experimental models but also are often the result of a lack of appropriate human pain phenotyping and the subsequent treatment of a heterogeneous subpopulation as well as problems with inadequate endpoints [4,15,16]. Additionally, pharmacokinetic properties, safety, and tolerability of the candidate compounds are crucial and the required therapeutic doses may not be achievable resulting from increased adverse events [17,18]. At least the issue of safety and potentially that of improved efficacy can be addressed by taking a complementary approach to drug development for painful conditions.

This additional avenue for the identification of novel analgesics may be offered by drug repurposing screens. Drug repurposing or repositioning is defined as the identification of new indications for existing drugs already in clinical use [19]. This approach has led to numerous new indications for drugs that are already approved, such as the use of propranolol, initially a blood pressure medication, for the treatment of pediatric hemangioma [20,21]. The pain field has benefitted from the fact that many drugs, used in a variety of pathophysiological contexts, such as the serotonin and norepinephrine reuptake inhibitor, venlafaxine, or the tricyclic antidepressant, amitriptyline, are currently used for the treatment of neuropathic pain states [22]. This suggests that other approved drugs may have analgesic or antihyperalgesic properties and that drug repurposing, in the context of pain pharmacotherapy, may lead to the identification of novel analgesics. In this regard, two questions arise:

(i) Are there any other drugs that are already approved and in clinical use for various indications that have been identified recently as potential antihyperalgesic or analgesic drugs in pathological pain states?

(ii) Are there central pathways or mechanisms in the pathophysiology of chronic and neuropathic pain that could be targeted in repurposing assays and rapidly tested for libraries of approved substances?

To address these questions, here we discuss recent novel findings suggesting that a number of already approved drugs such as ceftriaxone, metformin, minocycline, and pioglitazone that were originally developed for the treatment of entirely different pathologies have analgesic, antihyperalgesic, or neuroprotective effects that have been identified in preclinical studies using animal models of inflammatory or neuropathic pain. Some agents have been identified by serendipity in clinical practice, through sophisticated medical observation.

Repurposing of Approved Drugs as Analgesics

Do Antibiotics Have Antihyperalgesic Effects

A number of antibiotic drugs were reported in the 1980s and 1990s, on the basis of serendipitous and mechanistic studies, to exert antinociceptive effects as a result of inhibition of the metabolism of exogenous opioids and the enzymatic breakdown of endogenous opioids [23–25]. More recently, it has become clear that some members of this class of drugs have selective effects on neuropathic pain.

Previous findings, for instance, suggest a role for glutamate transporter GLT-1 upregulation in neuroprotection and reduction of excessive activity in glutamatergic synapses [26]. In the same study, ceftriaxone was identified as a potent stimulator of GLT-1 expression. In an animal model, systemic pretreatment for 7 days or systemic acute intraperitoneal treatment of rats with ceftriaxone alone (10–200 mg/kg) reduced carrageenan-induced mechanical hypersensitivity in the treated rats [27]. Administered together with ibuprofen, paracetamol, celecoxib, or levetiracetam, ceftriaxone acted synergistically to reduce the nociceptive hypersensitivity. GLT-1, the human ortholog of which is excitatory amino acid transporter 2 (EAAT2), is