Advancements in the treatment of pain: not all opioids are the same

Robert B. Raffa[1,2,3,4,5]

[1]Professor Emeritus & Past Chair, Temple University School of Pharmacy, Philadelphia, PA; [2]Adjunct Professor, University of Arizona College of Pharmacy, Tucson, AZ; [3]Co-Founder, Enalare Therapeutics, Inc., Princeton, NJ; [4]CSO, Neumentum Inc., Summit, NJ; [5]Chief Scientist, Advantx Pharmaceuticals Inc., New York, NY, USA

ABSTRACT

In the heated discourse about the pros and cons of opioids, it is not uncommon to have them discussed as if there are no significant differences among them (except perhaps on the basis of potency, viz., the piperidine fentanyl and its structural analogs such as alfentanil, carfentanil, sufentanil, *etc*.). It thus seems timely and appropriate to reassess this perception. There are at least three "atypical" opioids approved for clinical use, and another in development, that in one way or another display a more favorable clinical profile than do the "typical" opioids such as morphine, oxycodone, *etc*.

Commentary

Treating pain is challenging, perhaps uniquely so in medicine. The proper treatment of pain requires modulation (attenuation) of pain pathways, rather than the elimination of pain sensation, since complete elimination eliminates detection of tissue damage (people born with a genetic insensitivity to pain are at much greater risk of injury).[1] A major evolved mechanism for pain sensation-perception attenuation is the endogenous opioid system, thus is a rational target for opioid analgesic drugs.[2]

The traditional, or "typical", opiates (e.g., morphine and codeine) and other morphine-like opioids interact with the endogenous opioid system to produce analgesia, but they also have well-known negative aspects (*e.g.*, respiratory depression, nausea and vomiting, sedation, constipation, immune suppression, and substance-abuse potential among others).[3] Decades of pharmacologic research have revealed that the actions of opioids are mediated *via* specific (opioid) 7-transmembrane G protein-coupled receptor (7-TM GPCR) subtypes (*e.g.*, mu-, delta-, kappa-OR) and 2nd-messenger pathways.[4,5] "Tweaking" of various aspects of the interaction with these receptors and pathways have been attempted in drug-discovery efforts to separate the desirable from the undesirable clinical characteristics of opioid analgesics.[6] Creative and impressive incremental advances have been made, but translation to drugs having major clinical advantage has been generally disappointing.

Simultaneously with the advances in the pharmacology of analgesics has been important advances in the understanding of the physiology of pain, normal and aberrant. Notable among these, for example, have been the development of insight into: gate control theory;[7] "wind-up" and sensitization (central and peripheral);[8] pain chronification (transition from acute to chronic);[9] the contribution of genetics and epigenetics and the microbiome;[10,11] among many others. Two of the most significant for an understanding and development of 'atypical' opioids has been the recognition of types of pain rather than just degree of pain, and elucidation of the pathways involved in the pain modulatory system known as diffuse noxious inhibitory control (DNIC).

Pain conditions were traditionally treated based on only one dimension – magnitude, or level. It was described with terms such as "mild", "moderate", or "severe", and the class of analgesic was chosen on that basis: *e.g.*, a non-steroidal anti-inflammatory drug (NSAID) or acetaminophen (paracetamol) for "mild"; codeine or similar or combination for "moderate"; and opioid for "severe". Such a classification scheme and decision-tree was sometimes adequate, but was often inadequate, leading to under- or over-dosing of one category of analgesic, when an-

Correspondence: Robert B. Raffa, PhD, 3825 E Diablo Canyon Pl, Tucson, AZ, USA.
E-mail: robert.raffa@gmail.com

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other would have been a better match.[12] It became clear that pains can differ in their underlying cause (physiology) as well as in their clinical intensity. It seems difficult to imagine that the pains from a puncture wound, blunt-force injury, snake bite, cancer, and a burn are identical. Therefore, an optimal pain treatment strategy would involve the matching of analgesic pharmacologic mechanism of action with the causative pain physiologic mechanism. A now-recognized common example of this is the general superiority of ibuprofen (an NSAID) vs opioids for treating dental-extraction pain (due to the anti-inflammatory action of NSAIDS such as ibuprofen and lack thereof with opioids).[13]

The second major shift in thinking about pain involved the recognition of the existence and physiologic advantage of modulation of the pain sensation. Important for messaging tissue damage, excess or unnecessarily prolonged signaling can be detrimental to addressing the immediate threat, and to recovery after an injury.[14] This led to greater appreciation and study of the endogenous modulatory pathways (DNIC).[15] And led to a shift away from an exclusively unidirectional ("ascending") injury ® pain model to a bidirectional model that incorporates a modulatory (attenuating, 'descending') pathway. Extensive research identified several major descending pathways, and neurotransmitter systems, such as adrenergic and serotonergic.[16] In addition to advancing the study of pain, the new findings of bidirectional pathways provided new opportunities for the discovery of analgesics that could target either the ascending or the descending pathways – or both. Those that target ascending opioid pathways plus one or more non-opioid descending pathways are the ones referred to as 'atypical' or 'multi-mechanistic' opioids.[17]

Two of the three currently FDA-approved multi-mechanistic opioids were discovered by serendipity (buprenorphine and tramadol) and the contribution and details of their multi-mechanistic pharmacology were discovered after their initial synthesis.[18,19] Tapentadol, the third, was designed from the outset to be a multi-mechanistic opioid.[20] Cebranopadol was also designed to be multi-mechanistic, and currently is in clinical development.[21]

Tapentadol is the one that was designed with the most straight-forward pharmacology, and for the greatest clinical simplicity, so it will be summarized as an example of the group. Tapentadol targets both the ascending opioid and descending non-opioid pathways. Its dual mechanisms of action are contained within a single molecule (not a racemate or in conjunction with an active metabolite), and it undergoes Phase 2 metabolism (not mediated by CYP-450, so fewer drug-drug interactions).[22] Regarding tapentadol's opioid component, it has about 10-fold greater binding affinity for the mu-OR (96 nM) than for the delta-OR (970 nM) or kappa-OR (910 nM).[23] Its binding affinity at the mu-OR is about 50-fold lower than that of morphine. Regarding its non-opioid component, tapentadol inhibits the neuronal reuptake of norepinephrine, with little effect on neuronal serotonin reuptake *in vivo*.[23] The two mechanisms of action interact synergistically in pain models,[24] yielding potency across a variety of pain models only 2- to 3-fold less than morphine despite its 50-fold lower affinity for the mu-OR.[23] Importantly, the synergistic interaction does not extend to adverse effects, as demonstrated for constipation,[25] thus providing a greater separation between therapeutic and adverse effect. Additionally, the non-opioid component targeting DNIC contributes to higher potency in models of neuropathic pain compared to typical opioids.[26]

Summary and Conclusions

"Typical" (traditional, standard) opioids have been available for decades (*e.g.*, oxycodone, hydrocodone, *etc*.) or even centuries (*e.g.*, morphine and codeine). Their ability to inhibit incoming pain signal transmission to the brain ('ascending' pathways) has been well known. But recent research of pain and analgesic physiology has revealed the importance of "descending" pain-modulatory pathways. This led to the recognition of a category of opioid analgesics that has actions on both "ascending" opioid pathways and "descending" non-opioid pathways. Two were recognized after being already used clinically and two were designed *de novo* (one in clinical practice, one in development). Each has a better clinical profile than traditional opioids.

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