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EDITORIAL

Suzetrigine: Is This What We Have Been Waiting for or Just the Beginning?

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With the opioid prescription crisis largely behind us and the ongoing illicit opioid crisis leading to tens of thousands of deaths each year, it leaves one to wonder, what other non-opioid pharmacotherapeutic options are out there to help our patients suffering with chronic pain? Though recent estimates are lacking, the economic impact of pain has been estimated to cost the USA close to $1 trillion, when adjusted for inflation, which is greater than the sum of heart disease, diabetes, and cancer.[1] Despite this staggering number, pain research remains underfunded, which may have led to an overall decrease in new therapeutics reaching the market. The most recent non-opioid pain medication, to be approved by the US Food and Drug Administration (FDA), celecoxib, went on the market in 1998, followed by the recall of a similar medication, rofecoxib, several years later due to an increase in cardiovascular events.[2] Understandably, the public and healthcare providers have remained cautious regarding novel medications coming to the market.

In 2018, the HEAL (Helping to End Addiction Long-term) Initiative was launched in an attempt to better understand pain mechanisms, encourage development of non-opioid therapeutics, enhance current pain modalities, and create safer interventions for those in pain.[3] With an annual budget of $500 million per year, the HEAL initiative has funded over $2.5 billion of research.[3] Although this initiative is still in its infancy, continued funding by Congress should be advocated to further pursue novel therapeutics given the impact of pain on society.

On January 30, 2025, the first non-opioid $Na_V1.8$ inhibitor (suzetrigine) was approved by the FDA. Based on prior studies, the $Na_V1.8$ sodium channels are selectively expressed in the peripheral nociceptive neurons of the dorsal root ganglia with the thought that inhibition would result in pain relief without the side effects associated with opioids.[4] To provide context to the need for continued clinical research and the long pipeline from discovery to clinical use, selective sodium channel inhibitors have been a proposed target for analgesia for nearly 20 years.[5,6] In two randomized controlled trials involving patients undergoing abdominoplasty and bunionectomy, the group receiving the 100 mg loading dose followed by 50 mg every 12 hours had greater pain relief over the course of the 48-hour post-operative period as compared to placebo.[4] Total adverse events were lower for this group compared to the placebo and opioid group, with no severe or life-threatening events occurring. Overall, there were fewer opioid-related side effects associated with suzetrigine, suggesting its safety when compared to opioids.

As physicians involved in managing pain, we recognize the importance of expanding our non-opioid therapeutic options. Pain is a complex condition with multiple contributing factors, and no single medication will serve as a universal solution. Effective pain management requires a multimodal, interdisciplinary approach, and it is important to critically

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assess both the potential benefits and risks regarding any new therapeutic in development and approved. While the approval of suzetrigine is a promising step forward, concerns and reactions of the medical community must be addressed along with countering misinformation, as some have made unfounded comparisons to medications, such as OxyContin, which was central in the prescription opioid crisis.

Despite suzetrigine's apparent safety, criticism remains regarding its lack of superiority against the opioid group, which is valid, yet it must be understood that its comparison against an opioid remains an unbalanced one given that its mechanism of action is different. First, opioids are centrally acting, which can produce a systemic effect of analgesia, whereas suzetrigine is peripherally acting. Opioids are less selective and may target multiple pathways, yet suzetrigine is more selective. Opioids do provide a more rapid and stronger onset, with hydrocodone-bitartrate having a time to peak plasma concentration of 1–2 hours with suzetrigine's being 4–6 hours. Non-opioid medications tend to have a ceiling effect with higher doses not necessarily resulting in better analgesia, although analgesia with opioids often produces greater analgesia with escalating doses, which is limited by adverse events. Given the concern by some in the medical community, suzetrigine is both structurally different than opioids and is not known to interact with the mu-opioid receptor, suggesting it has no effect on the mesolimbic dopamine pathway supported by no signs of dependence or addiction reported.[4] Given the short-term data on suzetrigine, Phase 4 post-marketing studies are needed to better understand the long-term effects, tolerability, and safety profile.

To address these concerns, studies with extended durations and follow-ups are needed to fully characterize the drug's efficacy and safety profile. Proper pain control post-operatively is key to improving outcomes and preventing the progression to chronic pain. By evaluating outcomes beyond 48-hours, investigators will be able to ascertain whether recovery is improved and the progression to chronic pain is reduced. Further studies focusing on related conditions to the mechanism of action of suzetrigine, such as neuropathy and acute exacerbations of chronic pain conditions, may provide those suffering from chronic pain some relief. It is important to frame the approval of suzetrigine as an addition to the armamentarium of the multimodal, interdisciplinary approach in managing pain rather than a panacea to replace all other medications. The approval of suzetrigine may have spurred a renewed interest in developing oral pain therapeutics, and with increased interest comes increased scrutiny, providing those who remain weary some relief of concerns.[7,8] The approval of suzetrigine is welcomed, as those who are treating pain are doing so with limited options.

Disclosure

Dr Michael Schatman is a senior medical advisor for Apurano Pharma, outside the submitted work. Dr Matthew Chung reports personal fees from Saluda Medical, outside the submitted work. Dr Trent Emerick owns stock/equity of Vanish Therapeutics, Inc, outside the submitted work. The authors report no other conflicts of interest in this work.

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