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EDITORIAL

Current Challenges and Potential Solutions for Targeted Drug Delivery (TDD) in Cancer Pain Management

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Enduring pain without sufficient relief can be overwhelming and profoundly impact a patient's quality of life. Among cancer patients, the prevalence of pain has been reported to be as high as 44.5%.[1] Whether caused by cancer itself or its associated treatments, pain can derail a patient's journey toward recovery and remission. Survivorship from cancer does not equate to immunity from pain, as up to 10% of cancer survivors continue to experience severe chronic pain.[2]

Despite advancements in treatment, detection, and prevention, the incidence of cancer continues to grow rapidly on a global scale.[3] Guidelines from the World Health Organization and National Comprehensive Cancer Network (NCCN) have previously recommended severe cancer pain to be treated with systemic opioids as the standard of care, although there are limited data on their long-term effectiveness and significant associations with adverse effects. The WHO has expanded upon the three-step analgesic ladder to a fourth step to include an interventional approach,[4] while the NCCN guidelines have expanded to include interventional strategies.[4,5] Although opioids remain central to cancer pain management, significant barriers hinder their use, including limited research to guide practice and policies addressing opioid misuse. Patients face access challenges such as dwindling reimbursement, state-specific compliance and regulatory barriers for controlled substances, escalating copays, and pharmacy shortages, which are further compounded by stigma and fears of addiction. Managing opioid therapy in this population presents unique challenges, particularly in balancing effective pain relief with systemic side effects such as sedation, lethargy, nausea, and constipation. These side effects can greatly impact quality of life and restrict the tolerable dosage of opioids. Additionally, the limited long-term effectiveness of systemic opioids, coupled with adverse effects such as hyperalgesia, tolerance, sleep disturbances, depression, and hypothalamic-pituitary axis dysregulation, underscores the pressing need for alternative treatment approaches. Targeted Drug Delivery (TDD) using Intrathecal drug delivery systems (IDDS) has yielded promising results in a randomized controlled trial, demonstrating its efficacy and safety as a treatment option for cancer pain.[6] However, registration data indicate a continual decline in the overall use of TDD in the last decade, irrespective of the indication. This decline was further impacted by the COVID-19 pandemic and supply chain disruptions in pump manufacturing, with few signs of resurgence.

The dwindling use of TDD creates a downward spiral; as interventional pain therapies expand, novel treatments often overshadow TDD, making it appear less appealing in comparison. This shift is unsurprising given the rapid expansion of pain intervention techniques. To ensure successful growth and development of TDD and avoid the current path towards eventual extinction of this critical therapy for our cancer patients, it is crucial for the field to address the significant challenges associated with its use.

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The diminishing use of TDD has also been evident in Accreditation Council for Graduate Medical Education (ACGME) pain fellowship programs across the country, further affecting the outlook and perceptions of future generations of pain physicians.[7] Many fellowship programs, like any other pain practice setting, face difficulties in collaborating with oncology groups and cancer centers due to the complex dynamics of cancer treatments and number of individuals involved in a patient's treatment team. This has resulted in challenges in fellowship education, where comprehensive training in cancer pain management, including intrathecal therapy, is often insufficient.[5] According to registration data from Medtronic, among the 118 accredited fellowship programs in the US, 49 had implanted at least one pump for cancer pain. The average number of cancer-related pump implants in the last year among those programs was 4.4 (mode of 1). Notably, cancer pain-related intrathecal implants in teaching institutions have declined by 54% between 2014 and 2024. In addition to formal academic training, variations in TDD practice among pain physicians highlight the need for enhanced mentorship to empower future generations through shared experiential learning.

Beyond large institutional settings, community-based hospital groups with compartmentalized treatment teams have demonstrated higher utilization of intrathecal pumps for cancer pain. Replicating this format across all practice types may be challenging. Institutional barriers, such as limited visibility of referring colleagues and complex infrastructure requirements (pharmacy coordination, nursing, refill coordinators, electronic medical records), make integration of TDD difficult. Additional challenges, such as transitioning patients comfortably to hospice, coordination of safe and timely pump refills, and the lack of a standardized algorithm for establishing a streamlined pump practice further complicates TDD integration.

Cost-effectiveness plays a crucial role in today's healthcare landscape, particularly as the industry shifts from a Fee-for-Service model to Value-Based Care. TDD has been a focal point of discussion regarding its economic viability. While some studies suggest that TDD may prove cost-effective over the long term, the broader economic impact remains a topic of debate. For instance, one economic evaluation determined that TDD is more effective but also more expensive than standard care, with an incremental cost-effectiveness ratio (ICER) of $57,314 per quality-adjusted life-year (QALY) gained.[8] In contrast, another study highlighted significant cost savings of $63,498 in the first year following implementation when combining targeted drug delivery with conventional medical management.[9]

The core challenge, beyond integrating or expanding a pump practice, lies in navigating the esoteric and complex regulatory requirements in offering TDD. The Controlled Substances Act (CSA) and Drug Enforcement Administration (DEA) regulations present significant challenges for pharmacies in delivering controlled substances to patients.[10] While pharmacies are allowed to deliver controlled substances to ultimate users through their employees, agents, or common carriers, the interpretation of "constructive transfer" has been a source of confusion. The DEA's stance on delivering patient-specific controlled substances to prescribing practitioners has evolved, creating uncertainty for pharmacies. Recent enforcement actions by the DEA have further complicated the regulatory landscape. In December 2023, the DEA ordered a pharmacy to cease shipping patient-specific controlled substances directly to practitioners, citing 21 CFR § 1306.07.[11] This action raises questions about the permissibility of such deliveries, even for medications administered under healthcare provider supervision. To navigate these challenges, pharmacies must carefully review their dispensing procedures to ensure compliance with the CSA and DEA regulations, potentially considering options such as obtaining power of attorney for constructive transfers or utilizing their own employees for actual transfers to ultimate users.

In a previous evaluation of cost and healthcare utilization for cancer patients, TDD was demonstrative of significantly lower cost and healthcare utilization compared to conventional medical management inclusive of systemic opioid use.[9] Despite these results, reimbursement continues to be a significant detriment for continued access and utilization. These barriers include the necessity (or lack thereof) for intrathecal trialing for this population, limited use of pharmacotherapy based on FDA labelling, and limited access for refills of certain medications by hospice agencies (ie, ziconotide).[12]

In a care team with many voices, cancer pain can be perceived as an acceptable norm and overlooked without a dedicated advocate. TDD is a dying art of cancer pain management which will need a concerted effort to systematically address identified barriers for its survival. This effort requires a collaborative approach from all pain societies or a mission-driven consortium to advocate for transformational reforms in education, training, regulatory compliance, reimbursement, and system-based challenges. We hope that our commentary on the current state of TDD for cancer pain will inspire key stakeholders to take meaningful and cogent steps forward.

Disclosure

Dr Matthew Chung reports personal fees from Saluda Medical, outside the submitted work. Dr Hemant Kalia is part of the speaker bureau for Averitas Pharma; consultant of Abbott, Nalu, SPR, Curonix, and Nervonic, outside the submitted work. Dr Michael Schatman is the senior medical advisor for APURANO Pharma, outside the submitted work. The authors report no other conflicts of interest in this work.

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