Exploring the Potential of Stem Cell Therapy and Non-Opioid Anesthesia and Pain Reduction: Reducing the Negative Impact on the Individual and Society

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Abstract
The opioid epidemic poses a significant public health challenge, stemming from the widespread misuse and abuse of opioids for pain management. Stem cell therapy (SCT) and non-opioid anesthesia emerge as promising alternatives to traditional opioid-based treatments, offering effective pain relief while mitigating the risks of addiction and overdose. SCT involves undifferentiated cells, which can differentiate into various cell types to promote tissue repair and alleviate pain. Non-opioid anesthesia employs techniques such as regional anesthesia and multimodal analgesia to manage pain during surgeries without relying on opioids.

Both SCT and non-opioid anesthesia demonstrate advantages in reducing opioid dependence and improving patient outcomes. SCT releases neurotrophic factors for neuropathic pain relief and can prevent opioid tolerance, while non-opioid anesthesia provides robust pain control with fewer side effects.

Although further research is needed to optimize their use, the integration of SCT and non-opioid anesthesia affords a comprehensive approach to addressing the opioid crisis. By reducing opioid prescriptions and promoting safer pain management practices, these interventions not only benefit individual patients but also alleviate the socioeconomic burden of opioid-related complications.
Ethical considerations, such as informed consent and patient autonomy, are essential in ensuring these alternative treatments’ responsible and equitable implementation. SCT and non-opioid anesthesia represent significant advancements in combating the opioid epidemic and improving public health outcomes.

**Abbreviations:** CPSP: Chronic Post-Surgical Pain; ESCs: Embryonic Stem Cells; HSCs: Hematopoietic Stem Cells; MSCs: Mesenchymal Stem Cells; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; OFA: Opioid-Free Anesthesia; PONV: Postoperative Nausea and Vomiting; QoL: Quality of Life; SCT: Stem Cell Therapy; TKA: Total Knee Arthroplasty

**Introduction**

**The Opioid Epidemic**

The opioid epidemic has emerged as a portentous public health crisis, bearing societal and individual repercussions. Opioids constitute a drug class primarily utilized for pain management, encompassing prescription pain relievers such as oxycodone, hydrocodone, and fentanyl alongside illicit substances like heroin. Originating in the 1990s in the United States, the opioid epidemic sprouted from escalated opioid prescriptions for pain relief. This surge in prescriptions fostered extensive diversion, misuse, and opioid addiction and overdose can induce respiratory depression, coma, and death. Beyond overdose risk, opioids are associated with serious adverse effects, such as sedation, nausea, vomiting, constipation, respiratory depression, and hypotension [2]. Moreover, opioid addiction can precipitate social deterioration and render individuals susceptible to other substance dependencies and risky behaviors [3,4]. Diverse policies and strategies have been employed to grapple with the opioid crisis, encompassing prescriber education, opioid prescription guidelines, medication-assisted treatment, opioid withdrawal interventions, and opioid-free anesthesia (OFA) [5,6]. Despite these endeavors, the opioid epidemic persists as an urgent public health crisis. Innovative and ongoing initiatives aim to explore alternative avenues for opioid prescription and management. Stem cell therapy (SCT) and non-opioid anesthesia stand as possible modalities to mitigate the opioid crisis by diminishing reliance on opioids for pain management [7,8].

**Explanation of SCT and Non-Opioid Anesthesia**

SCT utilizes undifferentiated cells that can develop into various cell types, including nerve tissue, cartilage, and bone [9]. Stem cells are classified based on their origin, which includes embryonic stem cells (ESCs) and adult stem cells. Adult stem cells branch into different types, such as mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and neural stem cells [10]. MSCs possess qualities that make them appealing for pain management, including their ability to differentiate and secrete therapeutic factors [11]. These factors, comprising anti-inflammatory cytokines, growth factors, and neurotransmitters, reduce pain and inflammation and accelerate tissue repair and regeneration [12]. MSCs demonstrate effectiveness in alleviating pain across various chronic pain models, including neuropathic and inflammatory pain [13]. Non-opioid anesthesia employs alternative methods for pain control during surgeries, avoiding reliance on opioids. Types of non-opioid anesthesia include regional anesthesia, local anesthesia, and multimodal analgesia. Regional anesthesia targets specific nerves to relieve localized pain, while local anesthesia involves direct injection of anesthetic agents into particular areas to alleviate pain. Multimodal analgesia combines different pain management strategies, including non-opioid medications and nerve blocks [5,14]. These approaches decrease the need for opioids during surgeries and lessen opioid-related side effects [5,6,15]. Both SCT and non-opioid anesthesia exhibit the capacity for pain reduction and enhancing patient quality of life (QoL) without opioid reliance. Notably, SCT demonstrates efficacy in preventing and reversing opioid tolerance and opioid-induced hyperalgesia in animal models [15]. Non-opioid anesthesia correlates with a reduced risk of opioid-related adverse effects like sedation, nausea, vomiting, and respiratory depression [5].

Opioids are associated with numerous adverse effects, including sedation, respiratory depression, constipation, and addiction, among others [1,5]. Thus, given the negative impact of opioids on individuals and society, there is a need to explore alternative approaches to pain management that could reduce the reliance on opioids.

**Discussion**

**Stem Cell Therapy (SCT) and Non-Opioid Anesthesia: Reducing Opioid Impact**

Two possible strategies, SCT and non-opioid anesthesia, offer promise in alleviating pain without relying on opioids. SCT has demonstrated efficacy in preventing and reversing opioid tolerance and opioid-induced hyperalgesia in animal models [11,15], possibly mitigating opioid misuse and addiction risks in patients...
renew. Stem cells have been shown to release neurotrophic factors that can help regenerate damaged tissues and alleviate pain symptoms. As a result, researchers have hypothesized that stem cells could help relieve chronic pain by regenerating tissues such as damaged nerves, cartilage, and bone [21].

SCT has been explored as a treatment option for various types of chronic pain, including neuropathic pain and musculoskeletal pain. SCT has been shown to relieve chronic pain, primarily by promoting tissue repair and regeneration and reducing inflammation. An increasing body of evidence suggests that SCT is a viable and effective treatment option for most musculoskeletal and orthopedic issues [21]. Studies have shown that SCT is an alternative to invasive surgical procedures and more addictive treatments like opioids [11,19–22].

Research has demonstrated the therapeutic effects of stem cells in reducing pain and improving patients' QoL. However, further exploration is needed to understand more fully the optimal dosing and timing of SCT and the use of stem cells in different types of chronic pain, as well as the ethical considerations surrounding stem cell research and treatment, including issues related to informed consent, transparency, and safety [21,23].

**Pain Reduction Research**

SCT has been explored as a treatment option for various types of chronic pain management, including neuropathic pain, musculoskeletal pain, and lower back pain [21].

SCT for pain reduction is an active area of research, with numerous ongoing clinical trials and studies worldwide. These investigations vary in scope, focusing on different types of pain, stem cell sources, administration methods, and patient populations [24].

In a preliminary open-labeled study, SCT notably reduced pain intensity in patients with neuropathic trigeminal pain [25]. A phase II clinical trial involving 100 patients demonstrated that stem cell injections into degenerative discs led to decreased low back pain persisting for at least 12 months [26]. Another clinical investigation evaluated SCT for chronic pain conditions, including lower back pain, neurologic pain, and musculoskeletal pain, revealing improvements in pain symptoms and patient QoL [27].

**Limitations and Risks**

Stem cell-based therapies pose severe limitations and risks (Table 1). Significant limitations include the challenge of directing stem cells to differentiate into specific cell types. Although stem cells can differentiate into various tissues, uncertainties persist regarding their self-renewal and differentiation capacities [28]. The quantity of stem cells that can be procured from an individual may be constrained [29]. Stem cell-based therapies require further research to determine optimal dosing and timing for maximizing safety and...
efficacy [30]. Moreover, its limited availability and possible cost barriers pose challenges to its therapeutic usage [31]. Risks involve stem cells’ multipotent nature, which can lead to uncontrolled proliferation and the formation of teratomas or other tumors. Transplanted stem cells, especially if not derived from the patient, can trigger immune reactions, resulting in rejection and inflammatory responses [32]. The risk of infectious diseases exists due to possible contamination of the cells, accentuating the need for rigorous source tissue screening.

### Table 1. Limitations and Risks of Stem Cell Therapy (SCT)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitations</td>
<td><strong>Differentiation challenges</strong>: Directing stem cells to differentiate into specific cell types remains difficult due to uncertainties about their self-renewal and differentiation capacities.</td>
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<tr>
<td></td>
<td><strong>Limited cell quantity</strong>: The quantity of stem cells that can be procured from an individual may be constrained.</td>
</tr>
<tr>
<td></td>
<td><strong>Research requirements</strong>: Further research is needed to determine optimal dosing and timing to maximize safety and efficacy of stem cell-based therapies.</td>
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<tr>
<td></td>
<td><strong>Availability and cost</strong>: Limited availability and potential cost barriers pose significant challenges to its therapeutic usage.</td>
</tr>
<tr>
<td>Risks</td>
<td><strong>Uncontrolled proliferation</strong>: The multipotent nature of stem cells can lead to uncontrolled proliferation, resulting in teratomas or other tumors.</td>
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<tr>
<td></td>
<td><strong>Immune reactions</strong>: Transplanted stem cells, especially non-autologous ones, can trigger immune reactions, causing rejection and inflammatory responses.</td>
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<tr>
<td></td>
<td><strong>Infectious disease</strong>: There is a risk of infectious diseases due to potential contamination of the cells, necessitating rigorous screening of source tissue.</td>
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Non-Opioid Anesthesia

**Compared to Opioid-Based Anesthesia**

Non-opioid anesthesia involves the use of alternative pain management strategies during surgery, such as regional anesthesia, local anesthesia, and multimodal analgesia, that can reduce or eliminate the need for opioids. Unlike traditional opioid-based anesthesia, non-opioid anesthesia is not associated with significant respiratory depression, postoperative nausea and vomiting (PONV), pruritus, constipation, ileus, or delirium [5].

In recent years, non-opioid anesthesia has garnered attention amidst the ongoing opioid epidemic, aiming to curtail the risk of opioid misuse and addiction among surgical patients. Moreover, it has demonstrated superior pain control compared to traditional opioid-based approaches in various surgeries, including total knee arthroplasty (TKA) and shoulder surgery [33]. Alternative pain management strategies (e.g., multimodal analgesia that includes non-opioid compounds like acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], and local anesthetics) can reduce the need for opioids and associated adverse effects [33].

Several clinical studies show that opioid-free anesthesia (OFA) is beneficial for patients. However, there is no definitive consensus on the most optimal anesthesia techniques, and they may not be appropriate for all surgeries and patients [34]. Non-opioid anesthesia has several benefits compared to traditional opioid-based anesthesia. Considering the ongoing opioid epidemic, non-opioid anesthesia may provide a valuable alternative to opioids for effective pain management during surgery. However, further research is necessary to identify optimal techniques to maximize the safety and efficacy of non-opioid anesthesia.

**Pain Reduction Research**

Research indicates that non-opioid anesthesia effectively alleviates pain across various settings and procedures. For instance, lidocaine demonstrates efficacy as a neuroprotective agent, mitigating early postoperative cognitive dysfunction and neuropathic pain [5]. Comparative studies between opioid-free and opioid-based anesthesia reveal similar levels of pain reduction [35]. Non-opioid analgesics like acetaminophen and ketorolac prove effective in managing postoperative pain [36].

Beyond pain relief, non-opioid anesthesia offers advantages over its opioid-based counterparts. Studies report a reduced incidence of opioid-related adverse effects, such as respiratory depression. Furthermore, some research suggests a positive impact on cognitive function and decreased postoperative delirium [5]. However, OFA may not suit all patients or surgical types, as it presents drawbacks. Also, limited investigation into intraoperative analgesia depth has been noted in some studies [35]. Nonetheless, employing non-opioid agents within OFA regimens can significantly enhance safety during the perioperative and postoperative periods. While lidocaine and other non-opioid analgesics effectively reduce pain,
confidence in their ability to prevent chronic postsurgical pain (CPSP) remains low [37]. Current evidence suggests OFA’s effectiveness as an alternative to opioid-based anesthesia. It not only diminishes pain but also mitigates opioid-related adverse effects and enhances cognitive outcomes. **Limitations and Risks** Several limitations include the paucity of studies comparing the efficacy of intraoperative analgesia with non-opioid anesthesia (Table 2) [35]. Despite the availability of potent non-opioid analgesics with better side effect profiles and lower addiction risk, some contend that non-opioid strategies overlook gaps in evidence regarding their effectiveness [38]. Certain non-opioid analgesics, including lidocaine, ketamine, and gabapentinoids, have been linked to adverse effects such as sedation, drowsiness, and arrhythmia [39]. Opting out of opioids in the operating room may result in inadequate pain relief and increased rates of postoperative complications and hospital readmission [35,36]. Also, non-opioid anesthesia may require careful patient selection, as it may not be suitable for all individuals. Although concerns exist, studies generally support non-opioid anesthesia as a safe and effective alternative to opioid-based anesthesia for pain reduction, with few reported adverse effects [36]. Nonetheless, further research is needed to determine optimal protocols and settings for its application.

**Table 2. Limitations and Risks of Non-Opioid Anesthesia**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitations</td>
<td>Lack of comparative studies: There is a paucity of studies comparing the efficacy of intraoperative analgesia with non-opioid anesthesia.</td>
</tr>
<tr>
<td></td>
<td>Gaps in evidence: Some argue that non-opioid strategies overlook gaps in evidence regarding their effectiveness, despite the availability of potent non-opioid analgesics.</td>
</tr>
<tr>
<td></td>
<td>Careful patient selection: Non-opioid anesthesia may require careful patient selection, as it may not be suitable for all individuals.</td>
</tr>
<tr>
<td></td>
<td>Research requirements: Further research is needed to determine optimal protocols and settings for the application of non-opioid anesthesia.</td>
</tr>
<tr>
<td>Risks</td>
<td>Adverse effects: Certain non-opioid analgesics, such as lidocaine, ketamine, and gabapentinoids, have been linked to potential adverse effects including sedation, drowsiness, and arrhythmia.</td>
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<tr>
<td></td>
<td>Inadequate pain relief: Opting out of opioids in the operating room may result in inadequate pain relief and increased rates of postoperative complications and hospital readmission.</td>
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**Correlating SCT and Non-Opioid Anesthesia**

**Advantages of Each**

SCT and non-opioid anesthesia emerge as alternative approaches to managing chronic pain and reducing reliance on opioids. SCT presents a range of benefits, including the capacity to mitigate and reverse opioid tolerance, release neurotrophic factors for neuropathic pain relief, and can be sourced from the patient’s own body, lessening immune rejection risks [5,24].

Non-opioid anesthesia offers robust pain control with reduced addiction risk and more favorable side effect profiles. Currently available non-opioid analgesics hold promise in averting opioid addiction and overdose rates [5].

SCT and non-opioid anesthesia offer promising avenues for reducing opioid dependence and delivering effective pain management. Nonetheless, thoroughly considering their advantages and limitations before integrating them into clinical practice is required, as these treatments may not be universally applicable or suitable for all pain types. Treatment choices should be tailored to patients’ medical backgrounds, pain severity, and specific requirements [40].

**Combined Use for Pain Management**

Both SCT and non-opioid anesthesia exhibit individual promise in mitigating opioid dependence and delivering effective pain relief to patients. Specific SCT can release neurotrophic factors for neuropathic pain relief (see Supplementary Note) and reduce and reverse opioid tolerance [21]. Non-opioid anesthesia offers potent pain management with a diminished risk of addiction and more favorable side effect profiles than its opioid-based counterpart [5]. The combination of SCT and non-opioid anesthesia for chronic pain management has not been extensively studied. However, research suggests that combining non-opioid analgesics with SCT could provide an effective treatment option for patients with chronic pain by reducing the need for opioids [41–43].

While additional research is essential to evaluate the safety and efficacy of this combined approach, both treatments hold promise in diminishing opioid dependence and furnishing effective pain relief for chronic pain patients. They may also synergize with other non-invasive, non-pharmacological therapies like thermal treatments for optimized outcomes [44,45].

Table 3 overviews the advantages of individual and combined usage of SCT and non-opioid anesthesia.
Table 3. Advantages of Stem Cell Therapy (SCT), Non-Opioid Anesthesia, and Combined Use

<table>
<thead>
<tr>
<th>Category</th>
<th>Advantages</th>
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<tbody>
<tr>
<td>Stem cell therapy (SCT)</td>
<td>Mitigation of opioid tolerance: SCT has the capacity to mitigate and reverse opioid tolerance.</td>
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<tr>
<td></td>
<td>Neuropathic pain relief: Specific SCT can release neurotrophic factors for neuropathic pain relief.</td>
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<td></td>
<td>Reduced immune rejection risks: SCT can be sourced from the patient’s own body, lessening immune rejection risks.</td>
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<tr>
<td>Non-opioid anesthesia</td>
<td>Pain control: Non-opioid anesthesia offers robust pain control.</td>
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<td></td>
<td>Reduced addiction risk: Non-opioid anesthesia presents a diminished risk of addiction compared to opioids.</td>
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<tr>
<td></td>
<td>Favorable side effect profiles: Non-opioid anesthesia has more favorable side effect profiles compared to opioid-based anesthesia.</td>
</tr>
<tr>
<td>Combined use</td>
<td>Comprehensive pain relief: The combination of SCT and non-opioid anesthesia offers comprehensive pain relief by targeting different aspects of pain pathways and mechanisms.</td>
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<td></td>
<td>Reduced need for opioids: Combining non-opioid analgesics with SCT could reduce the need for opioids in chronic pain management.</td>
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<tr>
<td></td>
<td>Synergistic effects: Both treatments may synergize with other non-invasive, non-pharmacological therapies like thermal treatments for optimized outcomes.</td>
</tr>
<tr>
<td></td>
<td>Potential to diminish opioid dependence: The combined approach holds promise in diminishing opioid dependence and furnishing effective pain relief for chronic pain patients.</td>
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Ethical Considerations of Using Opioid-Alternative Treatments

**SCT Considerations**
Ethical considerations surrounding SCT for chronic pain revolve primarily around several key issues [46–48]:
- **Informed consent:** Ensuring that patients fully understand the nature of stem cell therapy, including its risks, benefits, and uncertainties, before providing consent for treatment.
- **Safety:** Safeguarding patients from adverse effects and ensuring that stem cell therapies are administered safely and regulated, with appropriate oversight by regulatory bodies.
- **Efficacy:** Ensuring that stem cell therapies for chronic pain are based on sound scientific evidence and have demonstrated effectiveness through rigorous clinical trials.
- **Source of stem cells:** Addressing ethical concerns related to the source of stem cells, including whether they are obtained from ethically permissible sources and whether their use harms donors.
- **Equity and access:** Ensuring equitable access to stem cell therapies for chronic pain, including consideration of issues related to affordability, availability, and distribution.
- **Transparency and accountability:** Promoting transparency in stem cell research and therapy, including disclosure of conflicts of interest, accurate reporting of outcomes, and accountability for any adverse events or misconduct.

Addressing these ethical considerations is essential to ensuring that stem cell therapy for chronic pain is conducted ethically, responsibly, and in patients’ best interests.

**Non-Opioid Anesthesia Considerations**
Ethical considerations surrounding non-opioid anesthesia for chronic pain include [49–52]:
- **Informed consent:** Ensuring that patients are fully informed about the nature of non-opioid anesthesia, including its benefits, risks, and alternatives, before providing consent for treatment.
- **Safety:** Ensuring that non-opioid anesthesia is administered safely and effectively, with appropriate monitoring and management of potential side effects or complications.
- **Equity and access:** Ensuring equitable access to non-opioid anesthesia for chronic pain management, including consideration of issues related to affordability, availability, and accessibility of alternative pain management strategies.
- **Patient autonomy:** Respecting patients’ autonomy and preferences in decision-making regarding pain management options, including their right to refuse or request specific treatments based on their values and preferences.
- **Education and awareness:** Promoting public and professional education about non-opioid anesthesia as a viable alternative for chronic pain...
management, including raising awareness about its benefits, limitations, and risks.

- **Research and innovation:** Supporting ongoing research and innovation in non-opioid anesthesia to improve its safety, efficacy, and accessibility for patients with chronic pain.

Addressing these ethical considerations is crucial to ensuring that non-opioid anesthesia is utilized ethically, responsibly, and in the best interests of patients with chronic pain.

**Societal Advantages in Addressing the Opioid Crisis**

The utilization of SCT and non-opioid anesthesia offers credible alternatives to combating the opioid dependence and abuse crisis (Table 4).

Firstly, SCT offers a promising alternative for managing chronic pain without the reliance on opioids. By harnessing the regenerative properties of stem cells, SCT can target the root causes of pain, such as tissue damage or inflammation, leading to long-term relief [53]. This approach not only reduces the need for opioid prescriptions but also minimizes the risk of opioid misuse, addiction, and overdose [54].

Similarly, non-opioid anesthesia provides an alternative pain management strategy during surgeries, effectively reducing or eliminating the need for opioids in perioperative care. By employing techniques such as regional anesthesia, local anesthesia, and multimodal analgesia, non-opioid anesthesia ensures effective pain control while avoiding the adverse effects and addictive potential associated with opioid-based anesthesia [16,33].

The combined use of SCT and non-opioid anesthesia presents a comprehensive approach to addressing the opioid crisis. By offering safe and effective alternatives for pain management, these interventions contribute to reducing the demand for opioids [1], thereby mitigating the risk of opioid dependence, addiction, and overdose in individuals undergoing treatment for chronic pain or undergoing surgical procedures.

Moreover, the widespread adoption of SCT and non-opioid anesthesia has broader societal implications. It can help alleviate the socioeconomic burden of the opioid crisis by reducing healthcare costs associated with opioid-related complications, emergency room visits, and addiction treatment programs [55]. Additionally, by promoting safer and more sustainable pain management practices, these interventions foster a culture of responsible prescribing and patient-centered care [56,57].

### Table 4. Stem Cell Therapy (SCT) and Non-Opioid Anesthesia and Their Societal Implications

<table>
<thead>
<tr>
<th>Category</th>
<th>Key Points</th>
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<tbody>
<tr>
<td>Stem cell therapy (SCT)</td>
<td>- Offers an alternative for chronic pain management without opioid reliance.</td>
</tr>
<tr>
<td></td>
<td>- Targets root causes of pain through regenerative properties.</td>
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<tr>
<td></td>
<td>- Reduces the need for opioids, minimizing the risk of misuse, addiction, and overdose.</td>
</tr>
<tr>
<td>Non-opioid anesthesia</td>
<td>- Provides alternative pain management during surgeries, reducing the need for opioids.</td>
</tr>
<tr>
<td></td>
<td>- Utilizes techniques like regional and local anesthesia for effective pain control.</td>
</tr>
<tr>
<td></td>
<td>- Avoids adverse effects and addictive potential of opioid-based anesthesia.</td>
</tr>
<tr>
<td>Combined use</td>
<td>- Presents a comprehensive approach to the opioid crisis by offering safe alternatives for pain management.</td>
</tr>
<tr>
<td></td>
<td>- Reduces demand for opioids, mitigating the risk of dependence, addiction, and overdose.</td>
</tr>
<tr>
<td>Societal implications</td>
<td>- Alleviates the socioeconomic burden of the opioid crisis by reducing healthcare costs and promoting responsible prescribing.</td>
</tr>
<tr>
<td></td>
<td>- Fosters a culture of safer and sustainable pain management practices.</td>
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</tbody>
</table>

The integration of stem cell therapy and non-opioid anesthesia represents a significant advancement in addressing the opioid dependence and abuse crisis. By providing effective alternatives for pain management, these interventions offer hope for individuals suffering from chronic pain while contributing to the collective effort to combat the opioid epidemic.

**Conclusion**

Stem cell therapy (SCT) and non-opioid anesthesia stand as promising solutions to the pervasive challenges posed by opioid reliance in pain management. SCT, utilizing undifferentiated cells with regenerative potential, has shown efficacy in preclinical studies, notably in preventing and reversing opioid tolerance and opioid-induced hyperalgesia. This approach holds promise for long-term opioid therapy patients and reducing addiction risks. Stem cells, sourced from tissues like bone marrow and adipose tissue, differentiate into diverse cell types, facilitating tissue repair and regeneration.
Non-opioid anesthesia employs alternative techniques such as regional anesthesia and multimodal analgesia to manage pain effectively without the adverse effects associated with opioids. Studies indicate its superiority in pain control compared to traditional opioid-based approaches, particularly in surgeries like total knee arthroplasty (TKA). The approach mitigates risks such as respiratory depression and postoperative complications while enhancing patient outcomes and quality of life (QoL).

Combining SCT and non-opioid anesthesia presents a comprehensive strategy to address opioid dependence and improve pain management outcomes. While both approaches offer individual benefits, their synergy remains underexplored. Preliminary evidence suggests that combining non-opioid analgesics with SCT could provide effective pain relief while reducing opioid usage. However, further research is warranted to optimize safety and efficacy in clinical practice.

Ethical considerations surrounding both treatments emphasize informed consent, safety, equity, and transparency. Addressing these concerns ensures responsible and patient-centered care delivery. Societal impact analyses highlight the ability of SCT and non-opioid anesthesia to alleviate the socioeconomic burden of opioid misuse by reducing healthcare costs and fostering a culture of responsible pain management.

**Conflict of Interest Statement**

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

**Supplementary Note**

Not all stem cells release neurotrophic factors. Neurotrophic factors are typically associated with specific types of stem cells, such as mesenchymal stem cells (MSCs) and neural stem cells (NSCs). These factors promote the survival, development, and function of neurons and are essential in processes such as neuroprotection and neural repair.

Mesenchymal stem cells, which can be sourced from bone marrow, adipose tissue, and umbilical cord blood, are known to secrete a variety of bioactive molecules, including neurotrophic factors like brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) [58]. Neural stem cells, which are found in the brain and spinal cord, also produce neurotrophic factors that support neuronal health and regeneration [59].

However, other types of stem cells, such as hematopoietic stem cells (HSCs), primarily focus on blood cell production and do not typically secrete neurotrophic factors [60]. Thus, the ability to release neurotrophic factors is not a universal characteristic of all stem cells but is specific to certain subtypes involved in neural support and repair.

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