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REVIEW ARTICLE

Methadone for Pain Management in Children with Cancer

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Abstract
Methadone is a synthetic opioid with unique pharmacodynamic and pharmacokinetic properties. It is effective in treating both nociceptive and neuropathic pain, which commonly co-exist in children with cancer. Upon reviewing the literature describing the use of methadone in pediatric oncology patients, publications are limited in number and low in quality of evidence; nevertheless, there is support for the safety and efficacy of methadone in treating pain in children with cancer, particularly when pain is refractory to conventional treatment. Although the risk of life-threatening arrhythmia is commonly cited as an argument against the use of methadone, our review of the literature did not support this finding in children. Further evaluation with prospective studies is warranted to develop evidence-based recommendations for the use of methadone in pediatric oncology.

Key Points

Methadone is effective for the treatment of cancer-related pain, which often has both nociceptive and neuropathic elements.

Existing literature supports the safety of methadone in pediatric patients despite its propensity to cause QTc prolongation.

1 Introduction

Methadone is a synthetic opioid with unique pharmacodynamic and pharmacokinetic properties that, somewhat paradoxically, both increase its clinical effectiveness and limit its widespread use. In addition to activating the opioid receptor subtype μ, methadone is an agonist at δ and κ opioid receptors [1], which results in a broader analgesic effect than that achieved by traditional opioids. Methadone acts as a moderate antagonist at the *N*-methyl-D-aspartate receptor [2] and strongly inhibits serotonin and noradrenalin reuptake in the central nervous system (CNS) [3], thereby modulating the sensation of pain through descending inhibitory pathways and allowing the attenuation of neuropathic pain of peripheral or central origin.

By and large, the complicating factors associated with methadone prescribing result from its complex pharmacokinetics. Methadone is a highly lipophilic drug with a large volume of distribution and highly variable elimination half-life [4, 5]. It is metabolized in the liver by cytochrome P450 (CYP) enzymes (primarily CYP3A4 and CYP2B6), creating the potential for drug–drug interactions via these pathways [6, 7]. Undoubtedly, the greatest drawback related to its use stems from its prolongation of the QTc interval and the associated risk of ventricular arrhythmia, a rare but potentially life-threatening adverse event [8–10].

Despite the shortcomings related to its use, methadone has found its way into the armamentarium of medications used to treat cancer pain in children (Table 1). Methadone is in many ways the ideal opioid for children with cancer pain. It is efficacious for both nociceptive and neuropathic pain, which commonly co-exist as a result of the disease itself and/or disease-directed therapies. It provides a long duration of analgesia and can be dosed as infrequently as

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Table 1 Methadone indications in pediatric oncology

Clinical indication	Example
Nociceptive pain refractory to conventional opioids	Visceral malignant pain due to metastatic solid tumors, graft versus host disease of the gut, or mucositis-related pain
Neuropathic pain refractory to first- or second-line agents (e.g., gabapentinoids, tricyclic antidepressants)	Chemotherapy-induced peripheral neuropathy
Mixed nociceptive and neuropathic pain	Solid tumors with nerve impingement or compression
Perioperative or postoperative use	Neuropathic pain associated with limb-sparing procedures or amputation
Prevention or reversal of opioid tolerance or opioid-induced hyperalgesia	Oncologic disease requiring chronic high-dose opioid therapy
Pain in the context of end of life	Progressive, metastatic disease requiring escalation of opioid therapy at the end of life

twice a day. It is the only long-acting opioid available in a liquid formulation, which is advantageous in young children who cannot swallow pills or when medications must be administered through a nasogastric or gastrostomy tube. For many children who require long-term opioid therapy, methadone may prevent or reverse opioid tolerance and opioid-induced hyperalgesia [11]. It causes less constipation than morphine [12] and is considerably less expensive than any other long-acting opioid available on the market [13] (Table 2).

In recent years, a compelling field of research has emerged that suggests an antineoplastic effect of methadone in addition to its known analgesic properties. Early work demonstrated that methadone, unlike morphine, does not suppress natural killer cell function [14]. Methadone has since been shown to inhibit the proliferation of lung cancer cells [15], induce necrotic-like cell death in neuroblastoma cells [16], induce apoptosis in myeloid and T-lymphoblastic leukemia cells [17], and enhance the cytotoxicity of treatment in some refractory leukemias [18, 19]. Given this emerging body of literature, as well as our personal experience using methadone in children with cancer pain, we performed a review of the literature on the use of methadone in pediatric oncology (Table 3).

A clinical librarian at St Jude Children's Research Hospital searched the PubMed, Web of Science Core Collection, and Scopus databases using the following terms: (methadone OR "methadone"[medical subject heading (MeSH)] OR "opioid tolerance" OR "opioid tolerant") AND pain AND (child OR children OR childhood OR pediatric OR infant* OR infancy OR adolescent* OR "young adult") AND (cancer* OR tumor* OR tumour* OR oncology* OR malignant*). The literature found to be relevant in the context of pediatric oncology is reviewed here.

2 Efficacy of Methadone for Cancer Pain in Children

The literature reflecting the use of methadone for pain in children with cancer is limited. Cumulative reports of methadone use for children with cancer pain, across the current literature, amount to a total of 66 children. A case series in 1998 reported on the use of methadone; of five

Table 2 Considerations in methadone prescribing

Advantages	Disadvantages
Potent opioid agonist [32]	Prolonged and highly variable half-life [5]
Multi-receptor analgesic activity [1]	Requires slow titration [35]
High bioavailability (oral and rectal routes) [4]	Numerous drug interactions [6]
Rapid onset of action [4]	Metabolism through cytochrome P450 system [6]
Long duration of analgesia [32]	Unpredictable conversion to and from other opioids [33, 34]
Lack of active metabolites [6]	QTc interval prolongation [10, 27, 28]
Availability in liquid formulation	Stigma associated with its use in treating addiction [32]
Lower incidence of constipation vs. other opioids [12]	
Low cost [13]	
Weak immunosuppressive effect [14]	
May possess antineoplastic properties [15–17]	

Table 3 Comparison of methadone dose regimens, opioid conversions, indications, and side effects

Study	Study type	*N*	Dose used	Conversion guidelines	Indication	Side effects
Shir et al. [20] (1998)	Case series	5	0.2–0.6 mg/kg/day	NS	Nociceptive pain refractory to opioids	Mild nausea
Sabatowski et al. [21] (2002)	Case report	1	Continuous infusion 4 mg/h (approx. 0.15 mg/kg/h) Bolus dose 5 mg (approx. 0.19 mg/kg) Lock-out 15 min	Morphine to methadone conversion 20:1	Poor analgesia, neurotoxicity	None
Bonertz et al. [22] (2007)	Case report	1	Initial dose 5 mg, followed by 2.5–5 mg q3–4 h. Transitioned to continuous IV infusion with initial concentration 0.22 mg/ml, titrated up to concentration of 0.32 mg/ml, run at a rate of 9–11 ml/h with 2 mg boluses given as needed via prefilled syringes.	NS	Poor analgesia with dose-limiting side effects	Vivid dreams
Davies et al. [23] (2008)	Case series	17	NS	Morphine to methadone conversion 1:2–60:1. IV at 80% of enteral dose if analgesia adequate; 100% if inadequate. IV dose given as 24 h infusion with breakthrough dose one-third to one times hourly dose. Recommended 0.1 mg/kg/dose if tolerance.	Poor analgesia, dose-limiting side effects	Somnolence, hallucinations, mild respiratory depression
Anghelescu et al. [24] (2011)	Retrospective cohort	41	Median range 0.06–3.8 mg/kg/day. Maximum dose 9.4 mg/kg/day	NS	Nociceptive pain refractory to opioids, neuropathic pain, opioid weaning, end-of-life pain management	Sedation, nausea, constipation, confusion
Amos and D'Andrea [29] (2013)	Case report	1	Chronic therapy 0.3 mg/kg/day	NS	Chronic pain related to GvHD	Central sleep apnea
Rasmussen et al. [25] (2015)	Case series	2	Case 1: median initial dose 0.4 mg/kg/day. Maximum TDD 32.7 mg/kg/day Case 2: median initial dose 1.0 mg/kg/day. Maximum TDD 24.8 mg/kg/day	NS	Severe neuropathic pain unresponsive to opioids	Drowsiness, abstinence symptoms with withdrawal, hypotension, CNS depression, QTc prolongation
Gjedsted and Dall [29] (2015)	Case report	1	26.9–47.5 mg/kg/day	NS	NS	Hypoglycemia
Anghelescu et al. [27] (2016)	Retrospective cohort	37	Median dose 20 mg/day (range 5–125) or 0.37 mg/kg/day	NS	NS	Mild QTc prolongation, no arrhythmias

Table 3 (continued)

Study	Study type	*N*	Dose used	Conversion guidelines	Indication	Side effects
Madden and Bruera [26] (2017)	Case series	2	Case 1: 0.03 mg/kg/dose q12 h (0.06 mg/kg/day) Case 2: 0.04 mg/kg/dose q12 h (0.08 mg/kg/day)	NS	Severe neuropathic pain unresponsive to opioids	None
Madden et al. [28] (2017)	Retrospective cohort	25	Initial dose 0.1 mg/kg/dose q12 h (max 5 mg q12 h)	NS	Nociceptive, neuropathic, or nociceptive plus neuropathic pain not relieved with SA opioids, IV infusions requiring transition to LA opioid due to high MEDD	QTc prolongation > 500 ms in one patient, no arrhythmias

CNS central nervous system, *GvHD* graft vs. host disease, *IV* intravenous, *LA* long-acting, *MEDD* morphine equivalent daily dose, *NS* not stated, *QTc* corrected QT interval, *qxh* every x hours, *SA* short-acting, *TDD* total daily dose

children treated with methadone for pain, two had pain related to cancer diagnoses [20]. One patient was a 2-year-old (14 kg) male with metastatic nephroblastoma and severe abdominal pain due to liver metastases. He was initially treated with morphine, which provided minimal pain relief. The treatment was transitioned to oral methadone [1.5 mg orally three times a day (TID) and two optional 0.5-mg doses]. Within a day of starting methadone, pain ratings decreased from severe to mild. He remained on oral methadone for 36 days (discontinued 2 days before his death), with daily doses not exceeding 6 mg. He remained pain-free and alert until the time of death. Another patient was a 5-year-old (18 kg) female with acute lymphoblastic leukemia (ALL) who developed severe abdominal pain when being treated with endoxan and 6-mercaptopurine. The pain was not relieved with morphine. She was placed on oral methadone (2 mg TID with a parent-controlled escalation up to 3 mg 4 times a day) and remained on methadone for 10 days. There was dramatic reduction in her pain during hospitalization, and she was discharged home with a prescription of oral acetaminophen.

A case report in 2002 described an 8-year-old male (26 kg) with advanced metastatic neuroblastoma who had mixed nociceptive and neuropathic pain due to tumor progression [21]. Pain was refractory to treatment with intravenous morphine patient-controlled analgesia (PCA) despite titration to a maximum dose of 2450 mg daily. At this dose, he experienced signs and symptoms of opioid neurotoxicity (e.g., myoclonus, hallucinations, and cutaneous hyperalgesia), and morphine was replaced with L-methadone at a conversion ratio of 20:1. The patient was given L-methadone PCA at a basal rate of 4 mg/h and bolus of 5 mg every 15 min. No loading dose was given before starting PCA. He experienced considerable improvement in analgesia within 24 h of methadone initiation, and opioid-related side effects resolved with 72 h. Although demand dosing increased, he continued to experience good pain control without opioid-related side effects until death 1 week later.

In 2007, a case report described a 6-year-old female with widely metastatic liver cancer who experienced severe neuropathic pain due to nerve compression from pelvic metastases [22]. Oral morphine at 400 mg/day provided inadequate analgesia despite high sedation. She was prescribed oral methadone at an initial dose of 5 mg, followed by 2.5- to 5-mg doses every 3–4 h. She experienced dramatic improvement of pain levels within 36 h of methadone initiation as well as considerable improvement in mental status. She continued this regimen for 3 weeks until she could no longer tolerate oral medication, at which point methadone was given as continuous intravenous infusion (initial concentration 0.22 mg/ml, titrated up to concentration of 0.32 mg/ml, run at a rate of 9–11 ml/h, with 2-mg boluses given as needed).

She received intravenous methadone via continuous infusion for 8 days before dying peacefully at home.

A case series in 2008 reported 17 children [median age 8.9 years (range 2.6–18.6)] with advanced cancer treated by opioid rotation from primary opioids (morphine, hydromorphone, and fentanyl) to methadone because of poor analgesia or dose-limiting side effects [23]. Of them, 13 (76%) had solid tumors (neuroblastoma being the most common), three had hematologic malignancy diagnoses, and one had a brain tumor diagnosis. Conversion ratios from morphine to methadone ranged widely from 1:2 to 60:1, depending on the duration of time of opioid treatment and the morphine equivalent daily dose (MEDD) during the week before conversion. Methadone was given orally to 11 patients and as intravenous infusion to six patients either because they refused or could not tolerate enteral medications. Intravenous methadone was dosed at 80% of the enteral daily dose if analgesia was adequate and at 100% if analgesia was inadequate at the time of rotation. The intravenous dose was given as a 24-h infusion, with breakthrough doses between one-third and one times the hourly dose as parent-controlled analgesia. Parents reported improvement in analgesia in 16 (94%) children, with one patient experiencing poor analgesic control until the time of death. Functional status improved in four (24%) patients. Methadone was discontinued in one patient due to adverse effects (e.g., somnolence, hallucinations, mild respiratory depression), which had also occurred when morphine was administered. Electrocardiography was not performed as the need for improved analgesia outweighed the risk of QTc prolongation. The authors recommended dosing methadone at 0.1 mg/kg/dose (as if opioid naïve) in patients demonstrating tolerance.

A retrospective study published in 2011 evaluated the use of methadone in 41 pediatric patients [mean age 15.7 years (range 0.6–23)] with primary oncologic or hematologic diseases [24]. Methadone was administered for at least one of the following indications: nociceptive pain unresponsive to other opioids [$n = 17$ (33%)], neuropathic pain [$n = 20$ (39.2%)], facilitation of opioid weaning [$n = 11$ (21.6%)], and end-of-life pain management [$n = 3$ (5.9%)]. The most common diagnoses were leukemia [$n = 10$ (24.4%)], osteosarcoma [$n = 7$ (17.0%)], and rhabdomyosarcoma [$n = 5$ (12.2%)]. The most common cause for pain was post bone marrow transplant (BMT) pain [$n = 13$ (31.7%)]. The median starting dose of methadone was 0.32 mg/kg/day (range 0.06–3.8). The highest dose was 9.4 mg/kg/day, which was administered to an 18-month-old infant with osteopetrosis after BMT. The primary route of administration was enteral, with only three patients receiving intravenous methadone. Given the retrospective nature of the study, access to pain scores before and after initiating methadone was limited. Clinical charts indicated efficacy in 52.9% of patients with nociceptive pain and 40% of patients with neuropathic pain. The most common side effect was sedation, with no episodes of respiratory depression.

In 2015, a case series described the successful use of high-dose intravenous methadone for severe vincristine-induced neuropathy in two children [25]. One patient was an 11-year-old male with B cell ALL who was given methadone several times over his treatment course. The median initial dose of intravenous methadone after an interval without methadone was 0.4 mg mg/kg/day (range 0.02–4.9). The highest total daily dose (TDD) of methadone was 32.7 mg/kg/day and was given 182 days after the first day of methadone. Methadone provided effective analgesia (reduction of 4 points on the Numerical Rating Scale [NRS] on an 11-point scale), with two episodes of drowsiness and three periods of abstinence symptoms from withdrawal of the medication. Another patient was a 17-year-old female with relapsed Ewing sarcoma who also received intermittent methadone over the course of treatment. The median initial dose, following an interval without methadone, was 1.0 mg/kg/day (range 0.08–4.4). The highest TDD of methadone was 24.8 mg/kg/day. Methadone provided effective analgesia (reduction of 5 points on NRS). Side effects included one episode of hypotension and two episodes of CNS depression. QTc prolongation (510 ms) was observed with concurrent use of fluconazole and a tricyclic antidepressant. The QTc normalized after discontinuation of fluconazole.

In 2017, a case series indicated the efficacy of very low-dose methadone (VLDM) for treating severe neuropathic pain secondary to vincristine-induced neuropathy in two children [26]. One patient was a 19-month-old male with ALL who was in remission and on maintenance therapy with monthly vincristine (0.75 mg/m^2) as per the Children's Oncology Group protocol AALL-0631. He presented with refractory insomnia and delay in motor milestones and was diagnosed with vincristine-induced neuropathy. Treatment with several regimens that included amitriptyline and gabapentin was unsuccessful. He was then given VLDM (0.03 mg/kg/dose every 12 h) while continuing gabapentin (45 mg/kg/day). Within 1 week, his insomnia resolved. He remained on this regimen for 1 year, until completion of vincristine therapy. He was successfully weaned off both methadone and gabapentin over a 6-week period, without the return of neuropathic pain. The second patient was a 6-year-old male who also had ALL and received vincristine as maintenance therapy. He presented with progressive, severe lower-extremity and back pain that did not respond to treatment with gabapentin and morphine. He was given VLDM (0.04 mg/kg/dose every 12 h), which considerably improved his pain and functional status over the next 3 months and was not associated with adverse effects. He continued VLDM and gabapentin for more than 1 year while completing the course of vincristine.

3 Adverse Events Associated with Methadone Use

3.1 Cardiac Conduction Prolongation

Cumulative reports of implications of methadone use for cardiac conduction in children with cancer pain, across the current literature, amount to a total of 62 children. In 2016, a retrospective study of 37 children [mean age 16.1 years (range 0.9–27.4)] reported QTc prolongation among pediatric oncology patients receiving methadone [27]. Approximately 71% of patients had solid tumors. The median methadone dose was 20.0 mg/day (range 5–125) or 0.37 mg/kg/day. Mean QTc was slightly higher when patients were receiving methadone therapy than at baseline (446.5 vs. 437.55 ms). However, there were no correlations between methadone dose and degree of QTc prolongation or between treatment duration and QTc prolongation. Approximately 76% of patients received at least one concurrent QTc-prolonging agent without having any adverse effects. The most commonly administered medications were ondansetron, granisetron, and fluoxetine.

In 2017, a retrospective study examined the effect of methadone on QTc prolongation in 25 pediatric and adolescent oncology patients [median age 11 years (range 1–25)] with primarily solid tumors [16 of 25 (64%)] [28]. Patients received methadone if they had nociceptive, neuropathic, or mixed nociceptive and neuropathic pain that was not relieved with short-acting oral opioids or required transition from continuous intravenous infusion to long-acting opioids due to high MEDD. Methadone was initiated at a dose of 0.1 mg/kg/dose every 12 h, with a maximum of 5 mg every 12 h. Median QTc decreased from baseline after initiation of methadone. Transient QTc prolongation was observed in 4 of 25 (16%) patients. Only one patient had two consecutive episodes of QTc $\geq$ 500 ms, which occurred with concurrent use of other QTc-prolonging agents and improved by correcting electrolyte abnormalities.

The necessity of obtaining electrocardiograms (ECGs) in pediatric oncology patients undergoing methadone therapy for pain may be questionable in the presence of data suggesting that QTc prolongation is uncommon in children and while the only current recommendations and guidelines are limited to adults. Extrapolation from adult data to pediatric patients may generate a cumbersome, unnecessary practice and may reinforce the clinicians' hesitation in choosing methadone for treatment of cancer pain in children. Nevertheless, the concerns that would justify the clinical practice of following the QTc trends during methadone treatment for pain, especially with escalating dose regimens, include concurrent therapy with medications with QTc-prolongation effects or interaction with the metabolism of methadone and/or concurrent electrolyte abnormalities. There are no published reports of methadone-induced severe dysrhythmias in children treated for pain.

3.2 Rare Adverse Events

Other rare adverse events associated with methadone have been reported [29]. A case report described methadone-related central sleep apnea (CSA) in a 10-year-old male with acute myeloid leukemia who underwent two BMTs with total lymphoid irradiation. He was given long-term methadone therapy at a dose of 0.3 mg/kg/day for pain related to leukemia and graft versus host disease. At 10 months after the second transplant, he had hypersomnolence and nocturnal hypoxia with SpO_2 in the 70 s (mmHg) during a hospital admission. Polysomnography revealed severe CSA, with clusters of 2200 central apneas during sleep. Brain magnetic resonance imaging demonstrated ventricular dilatation with cerebral and cerebellar volume loss. Methadone dose was not weaned in order to better ascertain its contribution to the patient's CSA. The authors advised using caution in medically complex patients receiving chronic methadone therapy.

Another case report described hypoglycemia associated with the escalation of methadone dose in an 8-year-old girl (32 kg) with ALL [30]. Intravenous methadone was increased from a TDD of 860 mg/day (26.9 mg/kg/day) to 1560 mg/day (47.5 mg/kg/day). During that timeframe, blood glucose levels decreased from 6 to 12 mMol/l (106–216 mg/dl) to 1 to 1.5 mMol/l (18–27 mg/dl). Blood glucose normalized with a reduction in methadone dose.

4 Implications for Clinical Practice

In our review, methadone was noted to be a safe and efficacious agent for the treatment of cancer-related pain in children. By far, the most common clinical indication for using methadone was nociceptive, neuropathic, or mixed nociceptive and neuropathic pain that had not responded to μ opioid receptor agonists or other first-line therapies. In three studies [21–23], neurotoxicity and other adverse effects were additionally considered in the decision to rotate to methadone. Although opioid tolerance was noted or implied in several studies, it was not the sole indication to initiate methadone treatment. None of the studies reported the use of methadone as an adjunctive opioid-sparing agent. Only the study by Madden et al. [28] used methadone as an initial long-acting opioid, which possibly signifies the beginning of a trend to use methadone earlier in the treatment course.

Dosing regimens varied widely among the 11 studies, with one case series demonstrating the efficacy of VLDM,

which was lower than the recommended starting dosage of 0.1 mg/kg/dose for treating neuropathic pain related to chemotherapy-induced peripheral neuropathy [26]. The maximum TDD reported among the studies was 47.5 mg/kg/day and was associated with asymptomatic but considerable hypoglycemia [30].

Overall, side effects were mild and largely included nausea, constipation, confusion, and sedation [21, 23, 24]. More serious adverse events such as hypotension, CNS depression, hallucinations, and hypoglycemia were rare [25, 30]. One case report attributed CSA to methadone use but did not account for important confounders such as chemotherapy-related cerebral atrophy [29]. QTc prolongation was reported in three studies but was not clinically meaningful, with no documented arrhythmias even when QTc exceeded 500 ms [25, 27, 28]. While the correlation between methadone use and the development of Torsades de pointes (TdP) has been confirmed in adult patients [8, 9], the risk of TdP in pediatrics is less well established. To the best of our knowledge, there are no published case reports of methadone-induced TdP in the pediatric literature.

5 Limitations

The primary limitation of this review lies in the weak evidence generated by retrospective studies, the majority of which were case reports and case series, which by nature represent outliers and not general trends. The findings were primarily qualitative and difficult to compare across studies. The total number of studies was also limited, with only 11 primary sources of literature in pediatric oncology populations published in the past two decades. The limitation of findings from our review highlight the need for further investigations in a prospective manner.

Robust data on the use of methadone for cancer pain are lacking. A recent Cochrane review on the effectiveness and tolerability of methadone as an analgesic in cancer pain could not make recommendations on its use because of the poor quality of evidence [31]. The study conducted qualitative synthesis on six randomized controlled trials with a total of 388 participants; none of the trials included children. Based on risk of bias and sparse data, the quality of evidence was judged to be low. Evidence for specific adverse events was also judged to be poor because of a risk of bias, sparse data, and indirectness (i.e., use of surrogate outcomes). Given the challenges associated with dose titration and the potential for severe adverse events, the review concluded that methadone was unlikely to be first-line treatment for cancer pain.

6 Conclusion

In children with cancer, methadone may be more efficacious than other opioids in the context of severe nociceptive or neuropathic pain, when an intrinsically long-acting opioid is indicated; nevertheless, dosing and safety concerns may be associated with its use. Existing evidence suggests the safety and efficacy of methadone in pediatric patients for the treatment of cancer-related pain. Prospective trials investigating the use of methadone, particularly as a first-line long-acting opioid, are warranted in this patient population. The impact of methadone versus conventional opioids on oncologic outcomes also warrants further investigation.

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Compliance with Ethical Standards

Conflict of interest Catherine Habashy, Erin Springer, Elizabeth A. Hall, and Doralina L. Anghelescu have no conflicts of interest.

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