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ANESTHETIC TECHNIQUES IN PAIN MANAGEMENT (D WANG, SECTION EDITOR)

Buprenorphine for Chronic Pain: a Systemic Review

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Abstract
Purpose of Review The purpose of this review is to evaluate and explain our current understanding of the clinical use of buprenorphine in the treatment of chronic pain.
Recent Findings There has been few high-quality, unbiased studies performed on the use of buprenorphine in the treatment of chronic pain.
Summary Buprenorphine is an effective and safe analgesic that is tolerated at least as well, if not better, than other opioids. Given its safety and mechanistic advantages, the authors believe there is an important role for buprenorphine in the treatment of chronic pain severe enough to warrant the use of an opioid analgesic. Though data is lacking for superiority in chronic pain states, the other advantages of the molecule make it the preferential first-line opioid for around-the-clock pain in our practice.

Keywords Buprenorphine · Chronic pain

Introduction

Chronic pain is one of the most important public health issues we face in the USA, with direct and indirect consequences that trickle down and permeate society. The prevalence and financial costs of chronic pain eclipse any other health problem, affecting 100 million US adults at a cost of at least $600 billion annually [1] Chronic pain affects more Americans than heart disease, diabetes, and cancer combined [1].

Chronic pain is a complex disease that is typically described in terms of biological, psychological, and social inputs that affect the pathogenesis, chronicity, severity, and impact on an individual. Multimodal treatments for pain attempt to address each of these domains to synergistically reduce suffering and restore function in those affected by this disease. Although this paper will focus on the role of buprenorphine in the treatment of chronic pain, it is critical to remember that pharmacotherapy, especially with opioids, should be part of a broader pain care strategy that employs multiple modalities, including psychological (e.g., mindfulness meditation, cognitive behavioral therapy), rehabilitative, interventional, and complementary/alternative therapies.

There are over 200 medications that have been described in the treatment of pain, and only approximately 20 of these medications are opioids. Opioids are prescribed more than any other medication in the USA, with retail pharmacies dispensing nearly 215 million prescriptions in 2016 [2]. That corresponds to a rate of 66.5 opioid prescriptions per 100 persons, down from 72.4 per 100 persons in 2006 [2]. Between 2006 and 2016, the frequency of high-dose opioid prescriptions (> 90 morphine milligram equivalents (MME)/day) was reduced by 46.8% and continues to trend downward [2]. Despite this downtrend in prescribing, overdose deaths involving prescription opioids were five times higher in 2016 than in 1999 [3]. Opioid-induced respiratory depression can lead to fatal consequences and is the most common cause of medication-related fatalities [2–5].

Buprenorphine is an atypical opioid with a unique pharmacological profile that bears with it mechanistic and safety advantages in the treatment of chronic non-cancer pain. It displays partial agonist activity at the mu opioid receptor and has been shown to have a ceiling effect on hypoxic ventilatory response as compared to fentanyl [4, 6•]. Analgesic dosing is typically an order of magnitude lower than those utilized in medication-assisted treatment (MAT) for opioid use

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disorders. Buprenorphine does not demonstrate a ceiling effect in its analgesic effects, has a long half-life, and is available in several different formulations. This article will bring the reader up to date on the use of buprenorphine in the treatment of chronic pain through a critical review of recent literature and the expert opinion of the authors.

Buprenorphine Pharmacology

Buprenorphine is a schedule III controlled substance and is a derivative of the morphine alkaloid thebaine [6•, 7–9]. Buprenorphine has poor oral bioavailability of approximately 10% and as such is available primarily in non-oral formulations, including sublingual, buccal, transdermal, and intravenous routes of delivery. [9–12, 13••, 14] The transdermal formulation is approximately 75–100 times as potent as oral morphine, making it nearly as potent as fentanyl [8, 13••].

Buprenorphine is an atypical opioid with a mixed mechanism of action. It is a mu opioid receptor (MOR) agonist, as well as a kappa opioid receptor (KOR) antagonist and further demonstrates the ability to increase mu opioid receptor expression on cell membranes as a "chaperone" ligand [8]. At the MOR, it activates a different subset of the G protein than classical opioids such as fentanyl, morphine, and methadone [8, 13••]. Buprenorphine is also an opioid receptor-like 1 (ORL1) agonist, a property with advantageous ramifications. ORL1 activation provides analgesia at the level of the dorsal horn and reduces tolerance to opioids in the cortex [8, 13••].

Buprenorphine is classically described as a high-affinity MOR partial agonist, but this designation mischaracterizes the clinical effects of this medication. Pergolizzi et al. describe buprenorphine as a high-affinity MOR agonist with low intrinsic activity in vitro, leading to a ceiling effect on analgesia in some animal models and a ceiling effect on respiratory depression in humans [12]. However, there is evidence and experience that at clinically meaningful doses in humans, buprenorphine does not have a ceiling effect on analgesia but does maintain a ceiling effect on respiratory depression [4, 12, 13••, 15]. Due to its high affinity, buprenorphine does displace other MOR agonists and can precipitate withdrawal from that agent such that during buprenorphine induction therapy for MAT, patients are typically "rescued" from withdrawal with buprenorphine after a period of abstinence from other opioid agonists. At the doses used for pain treatment in our practice, we do not see clinical withdrawal with initiation of buprenorphine therapy concomitant with other opioids.

Dahan et al. compared the effects of intravenous buprenorphine and fentanyl on respiratory depression and analgesia in a randomized, double-blind, placebo-controlled trial in healthy human subjects [15]. The medication was infused over 90 s at doses up to 8.6 mcg/kg of buprenorphine and 7.1 mcg/kg of fentanyl, followed by recording of minute ventilation for 7 h [15]. They found a dose-dependent respiratory depression with fentanyl with apnea reported at doses greater than 2.9 mcg/kg and a time-to-peak effect of 4.8 min. Buprenorphine displayed a ceiling effect of respiratory depression at doses greater than 3.0 mcg/kg with no apnea reported in any buprenorphine subject and a peak effect of 117 min (see Fig. Fig.1) [15]. Doses as high as 1600 mcg/h of intravenous buprenorphine or 32 mg of sublingual buprenorphine have been reported without clinically significant respiratory depression [13••].

Multiple studies have confirmed that there is no ceiling effect to buprenorphine's analgesic effects in a clinically meaningful dose range [9, 12, 13••, 15, 16]. At doses of 3–6 mcg/kg, buprenorphine had a linear, dose-dependent analgesic effect to a nociceptive stimulus without any additional effect on respiration [15]. In a rat model, the odds ratio (OR) for analgesia and respiratory depression were calculated and utilized to calculate a safety index (OR(analgesia)/OR(respiratory depression)), which was 1.2 for fentanyl and 13.54 for buprenorphine [17]. In other words, buprenorphine has a therapeutic window more than ten times that of fentanyl, conferring a significant safety benefit to this compound. In 2014, Raffa et al. reviewed 24 studies to better characterize the analgesic efficacy of buprenorphine as a "partial agonist" as compared to "full agonist" comparators [18]. The authors found that in 23 of the 24 studies reviewed, buprenorphine produced an equianalgesic effect as compared to morphine, fentanyl, sufentanil, and oxycodone for the treatment of pain [18]. The authors conclude that buprenorphine does display partial agonist effects in terms of respiratory depression, but not in terms of analgesia, and propose that this is due to multiple mechanisms of analgesia and synergistic antinociceptive effects [18].

Classically, chief among the inevitable pitfalls of prescribing opioid medications is the development of tolerance (higher doses needed to achieve same therapeutic effect) and physical dependence (abrupt cessation of the medication results in withdrawal symptoms). Opioid withdrawal is not life-threatening but is a miserable experience with classic symptoms including flu-like symptoms (myalgias, rhinorrhea, chills), diarrhea, irritability, tachycardia, hypertension, restlessness, hot flashes, etc.. Tompkins et al. prospectively assessed spontaneous withdrawal from intramuscular buprenorphine 32 mg/day compared to intramuscular morphine 120 mg/day over a period of 18 days in healthy, out-of-treatment, opioid-dependent volunteers [19]. This was a double-blind, within subject comparison—meaning each subject was stabilized and withdrawn from both buprenorphine and morphine during the course of the 2-month study [19]. Withdrawal measures, vital signs, and pain scores were collected eight times daily and found to be significantly higher in morphine withdrawal with peak withdrawal effect at day 2 of withdrawal and normalization at day 7 [19]. During

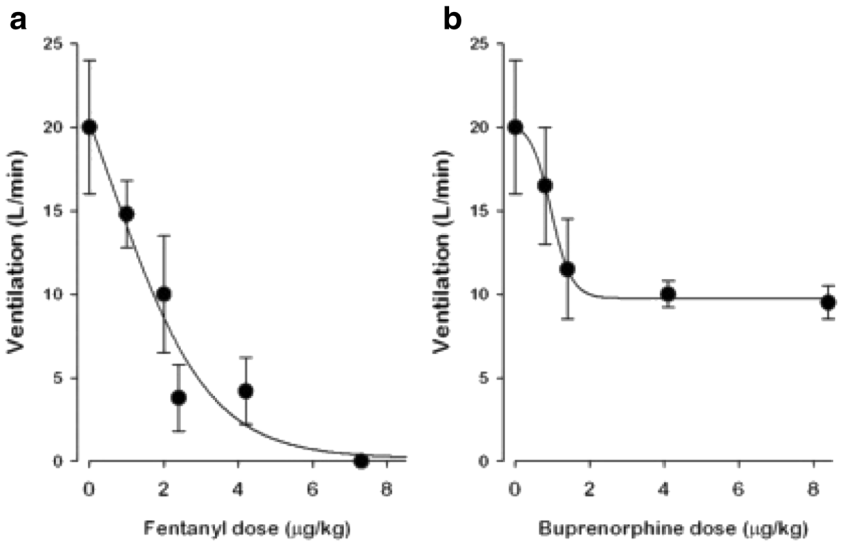

Fig.1 Dose-response relationships for fentanyl and buprenorphine on minute ventilation are consistent with dose-dependent respiratory depression in fentanyl (**a**) and a ceiling effect on respiratory depression with buprenorphine (**b**) used with permission from the publisher, SAGE Publications, Inc. [15]

buprenorphine withdrawal, there was minimal evidence of clinically significant withdrawal on objective and subjective measures (see Fig. 2), with no change from pre- to post-withdrawal states [19].

Buprenorphine for Opioid Dependence

Buprenorphine was approved by the US Food and Drug Administration (FDA) in 2002 for the treatment of opioid dependence, and since that time has become a critical component of MAT [16, 20, 21]. Sudden cardiac death occurs 4 times more often in methadone maintenance patients compared to buprenorphine maintenance [13••]. Furthermore, buprenorphine is not associated with QTc prolongation in MAT patients [13••]. Recall again that the doses used for MAT are substantially higher than those used to treat pain, and there is a long-term legacy of safety in high-dose use in the opioid use disorder population, making buprenorphine one of, if not the, safest commercially available strong opioid analgesics.

Buprenorphine for Chronic Pain

Buprenorphine is commercially available as a transdermal patch or buccal film for the indication of chronic pain requiring around the clock opioid treatment in doses ranging from 20mcg/h transdermal to 900mcg buccal every 12 h, respectively (Table 1). In this day and age, common sense and the 2016 CDC Guidelines provide guidance that the use of opioid medications for the treatment of chronic non-cancer pain should be stringently monitored and evaluated [5]. Opioids should be utilized in the treatment of chronic non-cancer pain as part of a balanced, multimodal program, and patient response to the medication should be closely monitored and only continued if efficacious. It is the author's practice to

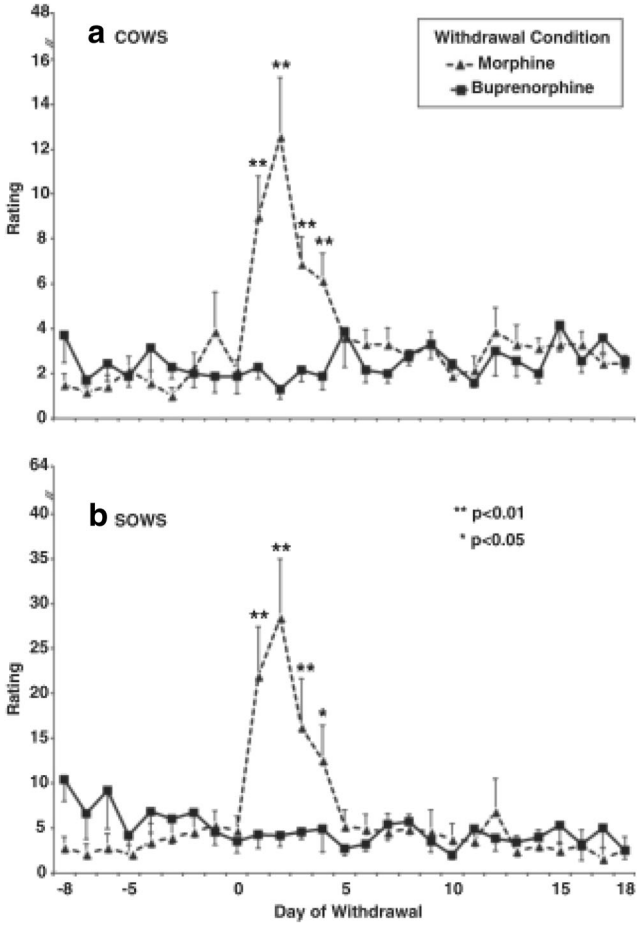

Fig. 2 Average daily Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS) ratings in subjects undergoing consecutive withdrawals after being stabilized on 32-mg/day i.m. buprenorphine and 120-mg/day i.m. morphine. COWS scores were measured by investigators whereas SOWS scores were reported by the subjects. Figure 2 used with permission from DA Tompkins, MT Smith, MZ Mintzer, CM Campbell, and EC Strain (2014) A Double Blind, within Subject Comparison of Spontaneous Opioid Withdrawal from Buprenorphine versus Morphine, J Pharmacol Exp Ther, 348 [2]: 217–226; DOI: https://doi.org/10.1124/jpet.113.209478 [19]

preferentially use atypical opioid molecules such as buprenorphine in the treatment of chronic non-cancer pain for which around-the-clock opioid therapy is required to reduce pain and increase function, so long as there are no treatment-limiting adverse effects. This common sense approach takes into account the unique mechanism of action and safety profile of the buprenorphine molecule, as well as the advantageous routes of administration that are inherently long-acting up to 7 days (Table 1).

Updates on Buprenorphine for Chronic Pain

Since 2015, five studies were identified that provide additional safety, efficacy, and tolerability data regarding the use of buprenorphine in the treatment of chronic non-cancer pain.

Yarlas et al. evaluated the impact of buprenorphine transdermal system (BTDS) on sleep in patients with moderate-severe chronic low back pain (CLBP) in two enriched-enrollment, randomized withdrawal, double-blinded controlled trials [11].

In the first trial, BTDS 10 and 20 mcg/h were compared to placebo in 541 opioid-naïve patients, and the second trial compared BTDS 20 mcg/h against a 5 mcg/h control in 441 opioid-experienced (30–80 MME/day for > 30 days) patients [11]. The authors utilized the Medical Outcomes Study Sleep Scale (MOS-SS), a validated patient reported sleep outcome measurement that assesses three domains (sleep disturbance, sleep adequacy, and daytime somnolence) and the validated Sleep Problems Index (SPI), which is reported as a *T score*, such that the mean is 50 and standard deviation is 10 [11].Patients in the first trial had a small but significant improvement in SPI (50.6 in the BTDS group, 48.3 in the placebo group) [11]. Patients in the second trial had a similarly nominal, but statistically significant, improvement in SPI at 12 week follow-up [11]. In both trials, all treatment and control groups were close to the population mean, questioning the clinical significance of these results.

Rauck et al. evaluate the efficacy and tolerability of buccal buprenorphine (BBUP) via a double-blinded, placebo-controlled, enriched-enrollment study in which 462 opioid-naïve patients with moderate-severe (NRS ≥ 5/10) CLBP were randomized and of whom 420 patients were included in the final analysis [24•]. During the open-label titration phase, approximately 15% of patients discontinued due to adverse events, primarily nausea [24•]. During the randomization phase, discontinuation was low (6.1% BBUP and 3% of placebo), and no cases of respiratory depression were reported [24•]. The titrated optimal dose in the study population was 150 mcg BID in 25.4% of patients, 300 mcg BID in 29.3% of patients, and 450 mcg BID in 45.3% of patients [24•]. Patients treated with BBUP were more likely to experience ≥ 30% pain relief compared to placebo (63 vs 47%); BBUP-treated patients reported higher global impression of change and used less rescue medication [24•]. However, it is interesting to note that there was no significant difference between BBUP and placebo in the number of patients achieving ≥ 50% pain reduction—placebo was quite effective in this study. [24•] The takeaway point from this trial is that 75 mcg BID is an appropriate starting dose in opioid-naïve patients, but nearly half the

Table 1 Buprenorphine formulations with an on-label pain indication

Route of admin.	Brand name	Approval date	Indication	Bioavailability	Dosages
Injectable (IV/IM)	Buprenex [10]	1981	Moderate to severe pain	100%	0.3 mg IV 0.3–0.6 mg IM
Buccal film	Belbuca [22]	2015	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate	46–65%	BID Dosing 75 mcg 150 mcg 300 mcg 450 mcg 600 mcg, 750 mcg 900 mcg
Transdermal system	Butrans [23]	2010	Moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time	15%	Weekly dosing 5 mcg/h 7.5 mcg/h 10 mcg/h 15 mcg/h 20 mcg/h

patients required 450 mcg BID in order to achieve significant analgesia.

The manufacturer of BTDS published a study in which the industry authors utilized Marketscan ® data from 2011 to 2015 to assess the utilization patterns in patients initiating BTDS [25]. The authors evaluated 31,533 adult patients with new prescriptions for BTDS during the study period and found that 88% had been dispensed opioids in the preceding 6 months prior to initial BTDS prescription, and 80% had concomitant (mostly) immediate-release opioid prescriptions while on BTDS [25]. Mean BTDS use was 100 days during the study period, during which 24% of patients reduced their total opioid burden from baseline mean 74.5 to 42.8 MME/day [25]. The authors conclude that in a subpopulation of patients, BTDS may lead to a reduction in overall opioid MME/day [25].

Simpson et al. evaluated the efficacy and safety of BTDS in patients with painful diabetic peripheral neuropathy in a double-blind, randomized, placebo-controlled trial in patients with moderate-severe pain for at least 6 months and stable glycemic control [26]. Of the 186 patients randomized (93 in each group), a high number withdrew due to adverse events (37/93 BTDS, 24/93 placebo), chiefly nausea and/or vomiting in the BTDS group [26] Patients who tolerated the drug did respond, with 86.3% of BTDS patients experiencing a 30% reduction in average versus baseline pain at week 12 as compared to 56.6% in the placebo group [26] The authors conclude that BTDS is an effective medication in the treatment of painful diabetic peripheral neuropathy, but that its clinical use is limited to those who tolerate the drug.

Yoon et al. evaluate the efficacy and tolerability of BTDS in Asian patients with chronic moderate-severe musculoskeletal pain titrated to a maximum dose of 40 mcg/h over a 6-week titration period and treated over 11 weeks [8]. This was an open-label study without an active or placebo control. The primary endpoint of pain score reduction was achieved, with an average improvement of 2.5 on an 11-point scale from a baseline of 6.2. [8]. Further, patients reduced the use of rescue medications (primarily acetaminophen and/or diclofenac) from an average of 5.2–5.7 tablets daily to 2.1–2.8 tablets daily [8]. The incidence of treatment-emergent adverse effects were high (78.1%), consistent with other studies, including nausea (39.5%), constipation (31.6%), dizziness (27.2%), somnolence (19.3%), emesis (16.7%), and skin reactions to the transdermal patch (6.1%) [8].

Author's Recommendations

With the availability of several novel delivery mechanisms bearing the on-label indication for chronic moderate-severe pain, it behooves the medical community to study and refine the use of the buprenorphine molecule for chronic pain. Given its safety and mechanistic advantages, the authors believe there is an important role for buprenorphine in the treatment of chronic pain severe enough to warrant the use of an opioid analgesic. The aforementioned studies and literature review lead to some practical recommendations for the clinician in practice. These recommendations represent the authors' opinion and practice pattern and are based on common sense with an emphasis on harm reduction.

Buprenorphine Is Recommended as the First-Line Long-Acting Opioid in Chronic Pain States

Unfortunately, the formulations with the on-label indication for pain can be inaccessible for patients due to coverage and cost issues. We urge payers to rationally revise their step edits and prior authorization requirements. It is not uncommon for payers to require patients to try and fail medications with dose-dependent respiratory depression (i.e., fentanyl, methadone, or extended release morphine) prior to approving buprenorphine. It is not sensible to require failure of multiple schedule II agents prior to approval of a schedule III agent, especially in light of the opioid epidemic and the 2016 CDC guidelines.

Buprenorphine Is Often Underdosed to Treat Pain in the Community

As board-certified pain specialists, the authors frequently are referred patients on subtherapeutic doses of BBUP or BTDS, typically initiated by primary care physicians or other non-pain specialists. The above studies and clinical experience dictate that most patients do not respond to the lower end of the commercially available dose ranges. These low doses are used to evaluate tolerability and to titrate to effect. They are not typically clinically effective.

Give Clear Titration Instructions to Your Patients and Monitor Closely

The authors typically start patients at the lowest or second-lowest dose of the available formulations with express instructions to double the dose if (a) there are no side effects and (b) there is inadequate or absent analgesia. The patients are seen in close follow-up to titrate the drug to effect. The majority of opioid-naïve patients (~ 45%) in the Rauck study required 450 mcg BID for analgesia [24•].

Future Directions

Various injectable forms of buprenorphine are being developed for opioid dependence and addiction. One form is an injectable depot formulation of buprenorphine using biodegradable polymer microcapsule technology [27]. An advantage of this formulation is minimizing risks of patient non-adherence or illicit diversion of the medication for opioid-use disorder patients. Various studies provide evidence of consistent delivery and pharmacodynamic activity of these formulations. In chronic pain patients with concern of adherence, cognitive issues, or other challenges in daily or weekly dosing, this formulation may provide options for patients. Misuse can be accidental as well as deliberate. These formulations should be considered in patients who are unable to manage their medications due to cognitive or other reasons. Some patients may not have reliable caregivers. Elderly patients with chronic pain may be a target for this unique delivery system, as they are also targets for diversion from caregivers and family members. Consider patients who have combined addiction and chronic pain condition that may be served with this delivery system. Furthermore, with the current climate surrounding opioid use and the general sentiment towards patients presenting in pain to acute care facilities, a depot formulation of buprenorphine lasting several days or a week may have benefits in reducing pain as well as reducing the number of opioid tablets dispensed. This would also have implications for postoperative pain management after outpatient surgery—an area that has come under scrutiny in terms of unused opioid medications in that setting. We look forward to seeing depot formulations of buprenorphine with various durations of action for acute, subacute, and chronic pain indications.

Another need is to further assess long-term benefit and consequences for buprenorphine for chronic pain more than a few months. In practice, for chronic pain syndromes with no available curative process, expectation is that buprenorphine will be utilized for palliation and for many years. Further studies are warranted for neuropathic and cancer pain conditions understanding the molecules unique binding to Mu, K, and delta receptors [13••]. A recent Cochrane review of buprenorphine for cancer pain was mixed in terms of benefit for cancer pain and recommends it as another alternative opioid [28]. Other authors have stated that buprenorphine have fewer side effects including less cognitive impairment and does not adversely affect the sphincter of Oddi [13••]. Further investigation is warranted to comparison studies to various opioid formulations for various chronic pain conditions, specifically in neuropathic conditions. Many have concern about potential QTc interval prolongation with buprenorphine, and further study is needed to determine the incidence and significance. It is also believe that buprenorphine does not adversely affect the hypothalamic-pituitary-adrenal axis and not as immunosuppressive [13••]. Supportive clinical studies are warranted as these effects are a major concern in long-term use opioids for chronic pain.

Compliance with Ethical Standards

Conflict of Interest Dr. Fishman reports personal fees and sponsored research from Medtronic, Inc. and Biotronik, Inc. He reports personal fees from Nevro, Inc. and Depomed and sponsored research from Stimgenics, LLC, all of which are outside the submitted work. Dr. Kim reports that he is on the speaker bureau for Jazz and Collegium. He is also a consultant for Medtronic and Biotronik, and has done research for Medtronic, Stimgenics, and Vertiflex. Dr. Kim is on the medical board of CBsync and Agrokind.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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