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THE LEADING SOURCE FOR PERIOPERATIVE HEALTH CARE NEWS

ASA Survey Results:

Commercial Fees Paid for Anesthesia Services – 2022

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ASA is pleased to present the annual commercial conversion factor survey for 2022. Each summer, we survey anesthesiology practices across the country. We ask them to report up to five of their largest managed care (commercial) contract conversion factors (CFs) and the percentage each contract represents of their commercial population, along with some demographic information. Our objectives for the survey are to report to our members the average contractual amounts for the top five contracts and to present a view of regional trends in commercial contracting.

Summary

Based on the 2022 ASA commercial conversion factor survey results, the national average commercial conversion factor was $85.42, ranging between $81.22 and $89.52 for the five contracts. The

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Biased Signaling in G-Protein-Coupled Receptors: The μ Opioid Receptor

Richard Simoneaux Steven L. Shafer, MD, FASA
Editor-in-Chief

In 2012, the Nobel Prize in Chemistry was awarded to Robert J. Lefkowitz, Howard Hughes Medical Institute/Duke University Medical Center, and Brian K. Kobilka, Stanford University School of Medicine, for "groundbreaking discoveries that reveal the inner workings of… G-protein-coupled receptors" (asamonitor.pub/3Cb1vVL).

G-protein-coupled receptors are a group of proteins consisting of seven transmembrane strands that connect receptors on the inside and outside of the cell membrane. These proteins serve the vital function of allowing communication between the intra- and extracellular environments. G-protein-coupled receptors represent the largest family of mammalian proteins, and

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The 33% Problem: A Discussion With Hospital Executives

Catlin Nalley

It is one of the most enduring challenges faced by the specialty and one unique to anesthesiology – the discrepancy in Medicare payments for anesthesia services known as the "33% Problem". Whereas Medicare rates for other specialties represent between 75% and 85% of their commercial payment rates, payment for anesthesia services are less than one-third of commercial rates. In fact, it has been determined by some that the real number is likely now in the mid-20% range. ASA's economic experts have been working ceaselessly to address this issue since the early 1990s, soon after the flawed Resource-Based Relative Value Scale was established in 1992. Today, ASA continues to devote significant resources to the 33% Problem, including through our Payment Progress Initiative (asamonitor.pub/3Qi9WTk), and the issue has been explored extensively in the *ASA Monitor* (asamonitor.pub/3AmE76F).

This month, the *Monitor* reached out to two anesthesiology thought leaders who have long been intimate with the 33% Problem as both clinicians and health care executives. Below, Joanne Conroy, MD, President and CEO of Dartmouth-Hitchcock Health, and David Reich, MD, President and COO of The Mount Sinai Hospital, offer insights and possible solutions to the specialty's lingering 33% Problem.

As a hospital executive, what is your perspective on the "33% Problem?"

Dr. Conroy: "This is not a new issue. It has been going on for years, and there are several factors at play. Number one, I'm not sure that people completely understand anesthesiology billing, which is very

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PERIODICALS

In the Know: Biased Signaling

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their dysfunction is at the core of a number of pathologies (*Signal Transduct Target Ther* 2021;6:7).

G-protein-coupled receptors

Structurally, G-protein-coupled receptors comprise three distinct portions: the transmembrane domain, which includes seven alpha-helices that span the lipid bilayer of the cell membrane; the extracellular or the N-terminal domain, consisting of three loops; and the intracellular or C-terminal domain, also consisting of three loops.

The extracellularly facing portions of G-protein-coupled receptors can be stimulated by a number of different stimuli, including proteins, gases, neurotransmitters, amino acids, metal ions, and even light (photons) (*Curr Opin Struct Biol* 2019;57:196-203). Upon stimulation, a change is induced in the shape of the protein. The change translates to an action within the interior-facing portion of the G-protein-coupled receptor.

On the interior of the cell, the external signal can be coupled to different G proteins, or other proteins, termed *arrestins*, which can result in signaling via cyclic AMP (cAMP), inositol triphosphate, diacylglycerol, release of calcium ions, or the phosphorylation of protein kinases. This initial signaling by extracellular compounds is then translated to internal secondary signaling and ultimately leads to the physiological response.

The G-protein-coupled receptors present in humans are grouped into four different classes, based on their amino acid sequences: "A (rhodopsin), B (secretin and adhesion), C (glutamate), and F (Frizzled)" (*Signal Transduct Target Ther*. 2021;6:7; *Nat Rev Drug Discov*. 2019;18:59-82). So far, we have identified more than 800 human G-protein-coupled receptors. Of these, roughly 350 are deemed "druggable," meaning that they are potential therapeutic targets. Nearly half of the druggable G-protein-coupled receptors have been validated as legitimate clinical targets.

More than 500 FDA-approved drugs currently target G-protein-coupled receptors. As of 2021, approximately 60 compounds are also currently undergoing evaluation in clinical studies as G-protein-coupled receptor-targeted therapies (*Nat Rev Drug Discov* 2019;18:59-82).

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Opioid receptors

The opioid receptors are a group of class A G-protein-coupled receptors. There are three opioid receptor subtypes: delta (δ), kappa (κ), and mu (μ). Clinically, many opioid-based therapies selectively target the μ-opioid receptor. When activated, the μ-opioid receptor signals via the G-protein (Gαi/o and Gβγ complex) or β-arrestin (*Trends Pharmacol Sci* 2020;41:947-59). The Nobel Prize in Chemistry was awarded because Drs. Lefkowitz and Kobilka demonstrated how a ligand binds to the μ-opioid receptor can influence the balance between the drug effect coupled to the G-protein and the drug effect coupled to β-arrestin (*Sci Signal* 2021;14:677).

Once the μ-opioid receptor has been bound to a ligand, G-protein recruitment elicits biological effects such as analgesia, euphoria, and drug dependence. Recruitment of β-arrestin elicits biological effects such as respiratory depression, constipation, nausea, and vomiting (*J Pharmacol Exp Ther* 2017;361:341-8). Thus, it is thought that drug candidates with a bias towards G-protein recruitment would maximize the analgesia while minimizing some of the harmful side effects associated with β-arrestin recruitment.

Biased μ-opioid receptor agonists

The drug tramadol is administered as an oral tablet of two enantiomers ((+)- and (-)-tramadol). Following systemic absorption and metabolism, both enantiomers are converted into (+)- and (-)-desmetramadol by CYP2D6 (*Front Pharmacol* 2020;10:1680). Tramadol itself only weakly binds the μ-opioid receptor. Analgesia from tramadol is attributed to μ-opioid receptor agonism of (+)-desmetramadol. Interestingly, (+)-desmetramadol mostly spares β-arrestin recruitment. As a result, this (+)-tramadol metabolite is likely the first "biased opioid" that selectively elicits the G-protein-coupled opioid physiology versus the β-arrestin side effects. As noted by Zebala and colleagues, "relative to morphine {tramadol} is comparable to other G-protein biased μ-opioid receptor agonists, including the clinically tested oliceridine" (*Front Pharmacol* 2020;10:1680). Because of its dependence upon CYP2D6 for conversion to the biologically active desmetramadol, tramadol has a delayed onset in patients with normal CYP2D6 and may be completely ineffective in patients with CYP2D6 polymorphisms.

"Biased opioids may be as close as we ever get to the holy grail of opioid pharmacology. However, the advances are not limited to opioids. As Porter-Stransky and Weinshenker note, 'biased agonism complicates G-protein-coupled receptor activity, as different agonists at the same receptor can have opposing effects on physiology.'"

One of the most studied compounds in the biased μ-opioid receptor agonist realm is oliceridine (TRV-130) (*J Med Chem* 2013;56:8019-31). Medicinal chemistry and initial animal studies suggested that oliceridine was a biased μ-opioid receptor ligand with morphine-like analgesia but with a reduced risk of opioid-induced respiratory depression.

Oliceridine has a complex regulatory history. In 2018, the FDA narrowly declined (in an 8-7 vote) to approval oliceridine for clinical use. The FDA cited cardiac issues (Qt elongation) in their decision. However, they were also not convinced that it caused less respiratory depression in the clinical studies. In August 2020, the FDA approved oliceridine for "the management of moderate to severe acute pain in adults, where the pain is severe enough to require an intravenous opioid and for whom alternative treatments are inadequate" (asamonitor.pub/3QtaSob). This approval was for the short-term usage of intravenous oliceridine "in hospitals or other controlled clinical settings, such as during inpatient and outpatient procedures" but not for at-home administration. Notably, oliceridine retains the black box warning for opioid side effects, including life-threatening respiratory depression.

Trevena, the company that developed oliceridine, is also developing an oral biased opioid, TRV734 (*Clin Pharmacol Drug Dev* 2020;9:256-66). Preclinical studies demonstrated that TRV734 is a potent analgesic with reduced constipation risk relative to morphine. A first-in-human phase I study evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of TRV734 in healthy individuals (*Clin Pharmacol Drug Dev* 2022;11: 51-62). TRV734 was generally well-tolerated. The analgesia observed was similar to that of 10 mg immediate-release oxycodone.

Another biased μ-opioid receptor ligand is the compound PZM21 (*Nature* 2016;537:185-90). In their initial paper in *Nature*, the authors noted PZM21 was "more efficacious for the affective component of analgesia versus the reflexive component and is devoid of both respiratory depression and morphine-like reinforcing activity in mice at equianalgesic doses." Despite this promising initial report, subsequent studies found that PZM21 dose-dependently depressed respiration "in a manner similar to morphine, the classical opioid receptor agonist" (*Br J Pharmacol* 2018;175:2653-61).

Given its lack of selectivity for G-protein signaling, exploratory studies were undertaken, including the use of cryo-electron microscopy, to identify analogs of PZM21 that had diminished β-arrestin recruitment (*Chem Int Ed Engl* 2022;61:26). These studies led to the identification of FH210 as a potential clinical lead.

Discussion

The curse of opioids is that they can relieve almost any acute pain. No other

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The 33% Problem

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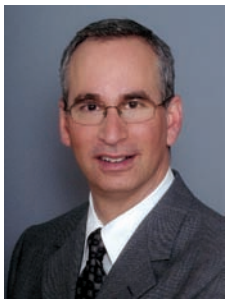
different than other billing processes. As a profession, we have debated for years whether or not to eliminate time units. Secondly, anesthesia delivers really important services, not all of which are reimbursed. We are a clinic model, and we pay for RVUs, but a lot of the RVUs are not reimbursed for many of our providers. Their activities, however, are very important to maintain and improve quality and access to care at our institutions. We could not run our inpatient services without these hospital-based specialties. In my opinion, insurers recognize this at some level. They know, whether or not they reimburse them appropriately, we will fill that gap so those providers actually have a market-competitive compensation."

Joanne Conroy, MD

Dr. Reich: "The issue of Medicare reimbursement is a longstanding problem in anesthesiology, and a key factor remains educating the public and policymakers on the critical role safe anesthesia services play in the health care of this nation. We must do our best to ensure the quality and quantity of anesthesia services don't decline as a result of this issue. Anesthesia departments and groups working with health systems must be up front about the challenges they are facing. To facilitate funds flow from a health system, it is important to exercise a high level of transparency and be willing to share details regarding income sources, including commercial and all federal payers. When the aggregate of all of the challenges faced by a department leads to a situation where a deficit might occur, it's time to have an honest discussion with the health system to see if a stipend can be negotiated based upon a verifiable and reasonable set of formulas."



David Reich, MD

How does this issue impact health care at an institutional level?

Dr. Reich: "Instability in an anesthesia department or group can lead to staffing challenges for perioperative and procedural services. As a result, the larger institution will suffer. Transparent communication regarding staffing requirements and fair market value analyses of regional and local reimbursement rates is critical so that facilities understand the issue and can help address provider needs. It is in a health system's best interest to have smooth operations, and anesthesia services are key to that."

Dr. Conroy: "Clinic models like ours pay based on our RVU. Whether they get paid for that RVU or not, they've delivered that service, and we make sure they get paid for it. When you have an exclusive contract with a private group, a different approach is taken. And so, the impact really depends on whether or not it is an integrated network or independent group. If you asked 50 CEOs who had independent medical groups with an exclusive contract, they would often say that the group that costs them the most is anesthesia. This can create a level of unnecessary conflict between the hospitals and anesthesia groups. I have seen more CEOs make bad decisions about their anesthesia groups than I have with any other specialty. It creates a level of conflict that can disrupt hospital operations. Therefore, it is important to identify and address the cause rather than just treating the symptom."

Do you have any advice for anesthesiologists contending with this issue in practice?

Dr. Conroy: "Anesthesiologists demonstrated their value during the pandemic. Even though surgical volume dropped, they were available and providing services in many other ways. Anesthesiologists stepped into leadership roles and many teams were securing airways and keeping everyone safe. Now is the time for anesthesia departments to cement the relationship – that is based on transparency and trust – with their facility partners."

Dr. Reich: "It goes back to having a seat at the table and being active participants in the operational concerns of the health system or hospital. Anesthesiologists are indispensable, but we have to demonstrate that on a daily basis, through our leadership in perioperative and procedural work. Be a key supporter of the organization. Be up front about workforce challenges. Recruitment and retention of anesthesiologists is a challenge. This is part of the reason why it's important to be at the table, so that all stakeholders can communicate their needs and work together to find solutions." ■

Catlin Nalley is a freelance medical writer with a degree in journalism from the University of Maryland. She has 10 years of experience covering a variety of medical specialties and is based in Jacksonville, North Carolina.

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Correction

An error appeared on page 21 of the August 2022 article "Antimicrobial Prophylaxis for Surgical Site Infection (SSI) Prevention." The dosage in the sentence "The cefazolin dosage in infants and children is similar to adults, i.e., 30 mg" was incorrect and should have read "30 mg/kg" We would like to thank ASA member Angela Camfield, MD, MS, FASA, for alerting us to this error.

In the Know: Biased Signaling

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systemic drug comes close to the analgesic efficacy of opioids. To the best of the authors' knowledge, there are no drugs of any class in preclinical or clinical development that are as effective analgesics as opioids.

Opioids have an extraordinary list of toxicities, including pruritis, ileus, itching, nausea, vomiting, urinary retention, respiratory depression, addiction, and death. This list of toxicities would be unacceptable with any other class of drugs. Opioids remain a mainstay of anesthetic and pain management for the simple reason that they work. In the case of severe pain, we often simply have no alternatives.

One of the holy grails of opioid research is finding an opioid that does not cause respiratory depression. Decades ago, it was hoped that identification of the μ_1 and μ_2 opioid receptor subtypes would lead to specific μ-opioid agonists that did not cause respiratory depression (*Life Sci* 1982;31:1303-6). The discovery of opioid receptor subtypes led to great pharmacology but no therapeutic breakthroughs.

Pasternak and colleagues also discovered that naloxonazine could antagonize morphine-induced analgesia but did not reverse morphine-induced respiratory depression (*Pharmacol Biochem Behav* 1986;24:1721-7). That's not very useful! However, finding an antagonist that selectively reversed opioid-induced analgesia led to years of work trying to find its inverse: a drug that reversed opioid-induced respiratory depression without reversing analgesia. No such drug was ever found.

Biased opioids may be as close as we ever get to the holy grail of opioid pharmacology. However, the advances are not limited to opioids. As Porter-Stransky and Weinshenker note, "biased agonism complicates G-protein-coupled receptor activity, as different agonists at the same receptor can have opposing effects on physiology." These authors note that other drugs, including oxytocin, cannabinoids, and psychostimulants, may have their normal responses altered with β-arrestin recruitment. This raises the possibility of the use of biased agonists as "potential therapeutics for addiction, analgesia, and other conditions." Since the oxytocin receptor (OXTR) is also a class A G-protein-coupled receptor that recruits arrestins, a biased oxytocin receptor may have applicability in the treatment of autism, depression, and PTSD (*J Biol Chem* 2012;287:3617-29). On a lighter note, such a compound might be a useful addition to the drinking water supply, as the last two-plus years have shown that we could all use a little more empathy and compassion. ■