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Buprenorphine Clinical Research & Practice: An International Perspective with a Focus on the Evidence of Opioid Efficacy in U.S. Pain Medicine Practice

Presented by Joseph Pergolizzi Jr., MD, Associate Professor – Temple University School of Medicine

EXECUTIVE SUMMARIES BY
MULTIVIEW

OVERVIEW

As Dr. Pergolizzi explains early in the session, “pain transcends global boundaries.” For physicians in the U.S. who are attending to patients with pain, opioid prescription has become a major issue in healthcare. Pergolizzi outlines the various components pain management, and offers insight the ever-evolving landscape of pain management.

CONTEXT

The purpose of this session is to introduce participants to the benefits of buprenorphine as researched by Dr. Joseph Pergolizzi Jr. and his colleagues. Opioids have become somewhat of a healthcare crisis, but as presented here, buprenorphine offers many quantifiable benefits as an alternative to opioids (such as morphine). The analgesic qualities, efficacy and safety of buprenorphine is examined in research with animal models, and the risk-benefit of several FDA approved buprenorphine products is presented.

AUTHOR BIOGRAPHY

Dr. Joseph V. Pergolizzi, Jr., Temple University Schools of Medicine, also serves as an adjunct assistant professor at Johns Hopkins School of Medicine. He is a senior partner for the Naples Anesthesia and Physician Associates Group of Southwest Florida, and has over 100 scientific papers and projects (either presented or published). He is an internationally recognized expert in many areas of advanced medicine including anesthesia, internal medicine, clinical research and drug discovery. He also is the editor for The International Journal of *Pain Medicine and Palliative Care*, the editor for *The Scientific World Journal of Anesthesia* and an invited feature editor for *Pain Medicine.*

1 CHRONIC PAIN MANAGEMENT HAS NOT IMPROVED

PREVALENCE AND INCIDENCE OF CHRONIC PAIN ARE INCREASING

One reason for the increase in chronic pain might be that the population pyramid is upside-down: Simply put, the general population is aging. With the advancement of disease research overall comes with a surge in pain management (because patients are living longer).

- The drugs available to HIV/AIDS patients 20 years ago are incomparable to what is on the market today. With more people surviving HIV/AIDS, there comes a need to manage pain.
- There is a strong effort to better the quality of life for cancer patients.
- A greater number of the elderly are staying active

There is “treatment inertia.” The average time it takes a patient to see Dr. Pergolizzi (who is a tertiary pain specialist) is 9 months – the patients usually have had symptoms of pain for 13 years.

RELIEVING PAIN IN AMERICA

The 2010 Patient Protection and Affordable Care Act required the Department of Health and Human Services to enlist the Institute of Medicine to examine the epidemic of pain in America. The study found that:

1. Chronic pain affects about 100 million adults.
2. Chronic pain actually affects more people than the total population suffering from heart disease, cancer and diabetes combined.
3. Pain costs the nation up to $635 billion each year in treatment (and lost productivity).

An interesting thing to note about these figures is that they do not include

numbers from the pediatric population.

CHRONIC PAIN IS MULTIFACTORIAL IN NATURE

We know that if we do not treat acute patient, a small portion of those patients will go on to suffer from chronic pain. Because of mal-adaptive neuroplasticity, pain becomes multifactorial in nature. For example, if a patient has pain in their hip, and then goes on to have a hip replacement, about 30 percent of those patients will still have pain after the hip has been removed. Why is that?

- Chronic pain is not monogamous: Patients come with other comorbidities.
- Chronic pain is a 24-hour problem. Dealing with pain is just like dealing with a diabetic patient: Control must be monitored over 24-hours in case there is an episode.
- Pain is a bio-psychosocial event. It's not just about the analgesics given.

2 THE VICIOUS CIRCLE

THE VICIOUS CIRCLE DEMONSTRATES INTERRELATION BETWEEN:

Insufficient analgesia, and side effects. Drug-drug interactions are not uncommon, and oftentimes the patient will develop analgesic tolerance.

INSUFFICIENT PAIN MANAGEMENT

It's not uncommon for patients seeing a new doctor to have experimented with a handful of different medications, which creates skepticism in which treatment to follow up with. There is a high rate of treatment discontinuations and a low rate of compliance.

So, what happens when either of those two occur? More pain.

When it comes to opioids, Dr. Pergolizzi refers to Thomas Aquinas: "Nothing is intrinsically good or evil but it's manner of usage may make it so."

Opioids are (realistically) our only option for pain. They don't cause end organ damage, but they have societal problems that are frightening – problems that involve all the stakeholders, from medical practitioners to legislative and government officials.

3 USING LONG-ACTING OPIOIDS TO TREAT MODERATE TO SEVER CHRONIC PAIN

RISK BENEFIT

- Chronic opioid therapy may be effect therapy for carefully selected and monitored patients with chronic, noncancer pain.

- Variability of patient response to different opioids
- Potential drug-drug interactions
- Potential side effects
- Opioid rotation
- Possibility of abuse, misuse, or addiction

OPIOID TREATMENT GUIDELINES

One of the common themes amongst guidelines is education. Educating the patient about the risk-benefit of the given opioid is essential, so that they may "own" their disease. It also takes a thorough history and examination of the patient to understand which medication will provide an optimal analgesic opportunity in this class.

STEPWISE APPROACH FOR PRESCRIBING OPIOID THERAPY IN NON-CANCER PAIN

1. Initial evaluation: Detailed medical history and physical examination; screen for risk of opioid abuse.
2. Referral: Refer patients at risk to specialist (addiction medicine or pain management).
3. Informed Consent: Establish an opioid agreement; discuss goals, expectations, risk, benefits and alternatives
4. Initiation: 4-8 week trial; tritrate close; decision to continue dependent on trial outcome
5. Monitoring: All COT patients; details dependent on risk status
6. Discontinuation: When treatment ineffective or abuse; taper

4 IS BUPRENORPHINE A GOOD OPTION IN CHRONIC PAIN MANAGEMENT?

BUPRENORPHINE

Buprenorphine has some interesting qualities that some doctors may not have considered before screening a patient to see if it would be a good option. For example, the majority of Buprenorphine is excreted through the feces. Since there is no dose suggested necessary for the renal-impaired or elderly, Buprenorphine is a good options for those two populations. Some other things to consider:

- Can be administered using a variety of routes including a transdermal patch
- N/V side effect can potentially be avoided or managed
- Titration may improve tolerability
- Simple and convenient

BUPRENORPHINE PRODUCTS APPROVED BY THE FDA

The product, formulation, approval date, and indication of four products are as follows:

- BUPRENEX: Injectable buprenorphine; 1981; Moderate to severe pain
- SUBUTEX: Sublingual buprenorphine; 2002; Opioid dependence
- SUBOXONE: Sublingual buprenorphine + naloxone; 2002; Opioid dependence
- BUTRANS: Transdermal buprenorphine patch; 2010; Moderate to severe chronic pain

4 ANALGESIC QUALITIES, EFFICACY AND SAFETY OF BUPRENORPHINE

REVIEW ARTICLE: CURRENT KNOWLEDGE OF BUPRENORPHINE AND ITS PHARMACOLOGICAL PROFILE

According to the literature, buprenorphine was very unique in various animal models. It showed analgesic effectiveness, which was also found in no susceptive and neuropathic type models. This was very interesting to Pergolizzi, since chronic pain has manifested over time as multifactorial in its etiology. The pharmacology of buprenorphine is as follows:

- Does not act as a “partial agonist” in analgesia terms
- (In animal models) it has been shown to produce a full analgesic effect that is dependent upon the intensity of the stimulus
- Radio-labeling studies in humans have demonstrated that full analgesia is produced at less than 100% of the mu-opioid receptor: The definition of a full agonist.
- Buprenorphine binds to and dissociates from the mu opioid receptor slowly.

ANTIHYPERANALLGESIA BY BUPRENORPHINE

Buprenorphine has some potential anti-hyperanalgesic effect. Therefore, it may be helpful across multiple types of chronic pain conditions. The larger the therapeutic index, the larger the “bandwidth effect,” meaning more people will receive an effect, and less people having a negative side-effect. To compare, **the therapeutic index for morphine is 464, while the index for buprenorphine is 12,313.** You also still have a similar analgesic efficacy with buprenorphine as you do with morphine.

Buprenorphine does not have an analgesic ceiling effect, but it does have a respiratory ceiling effect.

LOW DOSE TSD BUP IN CHRONIC LOWER BACK PAIN

In a clinical trial versus a placebo for lower back pain, Pergolizzi found that there was a statistically significant reduction in pain that also resulted in an improvement in sleep. Other research outcomes are as follows:

- 7 day-buprenorphine patches plus oral paracetamol were non-inferior to codeine/APAP tablets with respect to analgesic efficacy in older adult with OA pain in the hip/knee.
- Efficacy of 7-day buprenorphine patches was non-inferior to that of prolonged-release tramadol tablets.
- Buprenorphine is recommended as a first-line opioid in the elderly.
- No difference between patients >65 years and those being <50 years for pain reduction and side effects.
- No dose adjustment in the elderly required.

LD TDS BUP CONTRADICTIONS

- Patients who have significant respiratory depression, severe bronchial asthma, or known hypersensitivity to any of its components or the active ingredient, buprenorphine.
- Patients who have or are suspected of having paralytic ileus.
- Management of acute pain or in patients who required opioid analgesia for a short period of time, postoperative pain, mild pain, or intermittent pain (eg, use on an as-needed basis [prn]).