Levorphanol, Methadone, and the Management of Intractable Chronic Pain:

An Interview with Kerry Schmidt, BA, MBA; Jack P. McNulty, MD, FACP; and George B. Muller, RPh

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Abstract
For former National Football League player Kerry Schmidt, BA, MBA chronic pain is a part of everyday life. To repair sports related trauma sustained during his 6-year career as a defensive back, Schmidt has undergone 24 major orthopedic surgeries over the past three decades and will undergo two or three additional procedures to repair his lower back. Now a sports reporter, a syndicated sports columnist and a business owner, Schmidt says his pain at times has rated as 10 plus on a 10 point scale. Schmidt recently took control of his constant discomfort. After he consulted with Jack P. McNulty, MD, FACP, a specialist in the management of chronic pain, who collaborated with George B. Muller, RPh, a compounding pharmacist, Schmidt found relief with no adverse effects from the seldom-prescribed drug levorphanol.

Introduction

More than 30 years after Kerry Schmidt retired from professional football, the physical stress of rigorous competition continues to take its toll.

"I've been in pain 24/7 ever since I quit playing football in 1973," said Schmidt, who is 61. "Seven of my surgeries repaired damage caused by my being `speared' during a game, and all but one of my orthopedic injuries have been sports related. Over time, my bones haven't gotten any stronger. Until recently, the combination of injury and aging made the level of constant pain that I live with average about 6.5 on a standard pain scale.

"I'm averse to taking narcotics," said Schmidt. "Although the surgeries improved some of the pain, at one point I was taking 20 or 30 Advil (ibuprofen) tablets per day, and that provided only minimal relief. I decided that I wanted a physician specialist (not just a doctor who would give me pain pills) to manage my medication regimen and oversee its results. Both my orthopedic surgeon and my cardiologist recommended Dr. McNulty very highly. Before I started treatment as his patient 7 months ago, the pain in my back, hips, neck, knee, right wrist, and ankles would be extreme by the day's end, and it was getting worse over time. Everyday activities like climbing the stairs or getting dressed were becoming progressively more difficult. Constant pain really, really wears on you."

Jack McNulty conferred with Schmidt's surgeons and physicians, examined him, and reviewed his radiographs and magnetic resonance imaging results before prescribing a flexible regimen of pain control that has proven safe and effective. "Time-release levorphanol is the cornerstone of my treatment," said Schmidt. "When I first saw Dr. McNulty, the pain was pretty bad. He prescribed one 2-mg levorphanol tablet and one Percocet (acetaminophen and oxycodone) to be taken first thing in the morning, another tablet of levorphanol 8 hours later, and a third 8 hours after that. The first time I took those medications, I noticed relief within about an hour and a half: My pain level decreased from about 6.5 to a score of 1. I maintained that regimen for a month and then was able to decrease the amount of medication I was taking to one tablet of levorphanol and one Percocet twice daily. Now, I can usually stay ahead of the pain by taking just one tablet of levorphanol in the morning, plus one 10-mg tablet of Valium (diazepam) about twice per week to relax overtight muscles. I take Percocet only when needed as a rescue medication. I can often go 3 or 4 days in a row without taking any medicine, but I can resume or adjust my treatment if the pain level increases. Levorphanol works for me better than any other therapy has, and it's caused no significant side effects."

Discussion

As Kerry Schmidt attests, treatment with narcotic medications requires the judgment of a physician knowledgeable about the pharmacokinetics of controlled substances. For that reason, Dr. Jack McNulty is especially well qualified. Before he began his medical

career, first as an internist and then as a pain management specialist, McNulty was trained as a pharmacist. After he retired from his practice in general internal medicine, great personal loss engendered his abiding commitment to relieving the suffering of others. He founded a small private practice in pain management and established the Palliative Care Institute of Southeast Louisiana, a nonprofit community-funded educational foundation that presents programs on end-of-life care and chronic pain management for communities in Mississippi and Louisiana. Volunteer physicians from the institute staff instruct freshmen and sophomore medical students at the Louisiana State University School of Medicine and residents at New Orleans' Ochsner Clinic (the largest private healthcare organization in Louisiana) in those concepts. "That," said McNulty, "is the most significant aspect of our educational efforts. We physicians don't like to deliver bad news. We don't know enough about death and dying, and we tend to avoid that subject when we talk to our patients. End-of-life care and pain management are `orphan topics' in medical school; no department wants to address them. Most medical students never really focus on the treatment of terminally ill patients.

"Changing the attitudes and behaviors of established physicians is extremely difficult, but it's much easier to impart the principles of compassionate care and the proper management of pain to medical students and doctors in training. It's our goal to improve the education of the whole healthcare community (physicians, nurses, social workers, chaplains, and other caregivers) about the ethics and principles of pain management."

From Grief, Hope; From Suffering, Relief

What began for Jack McNulty as a volunteer effort has developed into a demanding second career. In 1999, after retiring from his medical practice in New Orleans, he and his wife moved to Covington, Louisiana. "I didn't want to stop working, but I knew that I didn't want to continue as a general internist," he said. "A month later, my son died of AIDS. He had been HIV positive for 13 years, and in his final weeks, he lived with us so that we could take care of him. As his disease progressed, that became more and more difficult, and the hospice of St. Tammany came in to help. We were absolutely amazed at how much they did for us. A team of professionals provided the physical care that my son needed, and the hospice staff was a tremendous source of emotional, psychological, and spiritual support when we were exhausted. They also used techniques for providing pain relief that I was unaware of, even after a long career in internal medicine. It was like having skilled family members who shared our burden of care, and we were better able to cope."

A few months after his son's death, McNulty began to volunteer as a hospice physician. "About that time, I read an article by oncologist Jerome Groopman on the subject of palliative medicine," said McNulty, "a new medical subspecialty that focused on relieving suffering and improving the quality of life for people with a terminal illness, and a light went on for me." After a year of study in palliative care and pain management with the American Academy of Hospice and Palliative Medicine, McNulty became very involved in providing hospice care. In 2000, he was certified as a palliative medicine physician and a trainer of other clinicians interested in that specialty. "I began to present local talks about end-of-life care in the hope that, somehow, we could change the medical system and make it possible for terminally ill patients (especially those in hospitals) to receive appropriate care and die with dignity," he said. Although McNulty's early attempts to engage the interest of local hospitals were unsuccessful, the general community (hospital volunteers, patients, and people who had attended his talks) pupported his goals. Through his efforts and contributions from the public, the Palliative Care Institute of Southeast Louisiana was founded in 2002. Every year since then, community-based funding for the Institute has increased, and relationships with the Ochsner Clinic and other medical teaching institutions have been expanded.

Managing Severe Nonmalignant Chronic Pain

"As I began my work in this new specialty," said McNulty, "I was most interested in providing palliative care, but eventually I began to get requests to treat patients with painful nonmalignant conditions. Although they were not at the end of life, I realized that their needs were the same as those of patients dying in pain: they were suffering, their lives were miserable, and their debilitating discomfort remained unrelieved."

To answer that need, in 2001 McNulty established a small consultative practice for pain management. He treats a very select population: those for whom the usual modalities (physical therapy, conventional drugs, steroids, epidural analgesics, nonsteroidal anti-inflammatory drugs) provide no relief. His patients have often suffered for years from polyarthropathy, fibromyalgia, or chronic low-back pain caused by multiple failed surgeries. "When I ask new patients to score their pain level on a scale of zero to 10," he said, "I also ask them to score their depression, anxiety, and anger. I inquire about their sexual function, their relationship with a spouse or significant other, and their frustration with the medical community. From their responses, it's easy to see how much their life has been disrupted by chronic pain."

"Orphan" Analgesics Prove Safe and Effective

Even before he established his second private practice, Jack McNulty was interested in analgesic therapies that were clinically sound but had been little appreciated. "In 2000, I read an article by Wheeler and Dickerson about the use of methadone or levorphanol in end-of-life care and chronic pain management," he said, "and I was impressed with its logic and the authors' arguments for prescribing Methadone, which blocks NMDA [N-methyl-D aspartate] receptors. Then in 2000, an article by Daniel Brookoff in Hospital Practice characterized chronic pain as a disease, not just a symptom. Brookoff addressed the neurophysiologic and neuropathologic effects of unremitting pain on the central nervous system and the resultant self-perpetuating pain cycle that can go on indefinitely. I was intrigued with that idea and began to consider prescribing methadone or levorphanol for some of my patients. Because of my long career as a general internist, I was not intimidated by the fact that pharmaceutical companies don't promote, market, or mention those medications. I began to carefully prescribe first methadone

and then (for those whose pain did not respond) levorphanol for the relief of intractable pain, and to my surprise, those drugs worked! They relieve neuropathic pain better than any other agent currently available. Often I've been able to easily convert a patient's treatment from thousands of milligrams of morphine daily to a minimal dosage of methadone. We've had no serious problems with almost 200 cases of such converted therapy, and it's very effective."

Compounding for Chronic Pain

For Jack McNulty, a fourth-generation pharmacist before he became a physician, the role of compounding in treating chronic pain is a favorite subject. "When I was studying pharmacy, all pharmacists were compounders," he said. "I still have the formula books that my father and grandfather used to make their preparations for medicines that weren't readily available. I grew up with the idea that compounding was part of the delivery of pharmacy services, and I still think along those lines today. When my compounder and I are problem solving, we communicate very well.

"Compounding is very useful in the preparation of analgesics, many of which have an unpleasant taste," said McNulty. "A mixture of raspberry with chocolate or mint can make the bitterest medication more palatable, and transdermal creams are especially useful for those who can no longer swallow. If rectal absorption is required, the compounder can prepare a dosage form that's effective and easy to administer.

"The versatility of treatment that compounding offers is quite remarkable. For example, one of my hospice patients with a life expectancy measured in weeks suffered from weeping malignant lesions on the chest, face, and neck. My compounder prepared an antibiotic-containing powder that, when applied with a puffer, adhered to the moist surface of the lesions and worked like a charm. There are many, many answers to therapy that compounding pharmacists can provide."

McNulty frequently collaborates with George B. Muller, RPh, the owner of the Compounding Corner in Lacombe, Louisiana. "George and I often work together to assist local hospice groups that aren't familiar with the use of methadone or levorphanol," said McNulty. "When a particular dosage form is required-whether it's a concentrate, a suppository, a transdermal, or a parenteral-that's when I need George the most. He is very interested in developing preparations that aren't commercially available, like the phenytoin-metronidazole paste that we use to heal decubitus ulcers. Long-term therapy with phenytoin is known to cause gingival hyperplasia. Phenytoin applied to the bed of a clean decubitus ulcer accelerates healing, apparently by stimulating the growth of blood vessels. Many ulcers refractory to all other therapy have resolved after treatment with that preparation. George has also formulated a transdermal analgesic cream containing ketamine, clonidine, lidocaine, and/or gabapentin, which is very effective. His problem-solving ability is a great asset; he's an essential part of the treatment team."

The Compounding Corner

George Muller is the owner and chief pharmacist of the Compounding Corner, a compounding-only facility equipped for the preparation of both sterile and nonsterile compounds. A member of the National Community Pharmacists Association, the International Academy of Compounding Pharmacists, and the board of directors of the Louisiana Pharmacists Association, Muller has been compounding in earnest since 1995. "I like to think of myself as a facilitator," he said. "I share information about effective pain-management medications with all my healthcare professionals, so that as many patients as possible can benefit."

When Jack McNulty became the director of a local hospice organization that used many of Muller's compounds, a great collaboration began. "We hit it off very well," said Muller. "Dr. McNulty is very open to trying new answers to patients' problems, and he calls on us frequently for dosage forms that aren't commercially available." Compounds containing methadone or levorphanol are common requests. "Methadone isn't manufactured in a concentrated liquid and certainly not in a solution that tastes good," said Muller. "It's our goal to enable patients to take as few doses of their pain medicine as possible, so we developed a liquid formulation in various concentrations (20, 40, or 60 milligram per milliliter) flavored with chocolate raspberry, which tastes good and has proven very acceptable to patients. We also prepare a levorphanol liquid concentrate in several sweet flavors, and we compound suppositories of both drugs in any and all strengths. Both levorphanol and methadone are effective in a transdermal cream, and we've had requests for that dosage form as well.

"About 75% of the patients we treat obtain relief from methadone, especially if the pain has a neuropathic component," said Muller. "Methadone targets both mu and delta pain receptors. Because it is effective in a lower dosage than morphine and produces fewer adverse effects, methadone is the better choice for long-term pain control. Levorphanol therapy is often the answer for patients who find treatment with methadone or morphine ineffective."

George Muller has developed his own formulations for liquid preparations of methadone and levorphanol, which are provided on page 12. "It's important that physicians be open to prescribing these drugs," he said, "both of which provide exceptional pain relief for patients whose suffering would be otherwise unrelieved."

Jack McNulty agrees. "The value and effective use of pharmaceutical compounding should be a part of continuing education for all physicians," he said. "It's clear that both methadone and levorphanol provide therapeutic advantages, particularly in the treatment of neuropathic pain, that conventional opioids do not offer. The use of those drugs in the management of chronic pain is finally garnering attention in the medical community. These drugs should be an integral part of the armamentarium of all physicians who provide palliative care and pain control."

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Formulations: Methadone or Levorphanol for the Management of Severe Chronic Pain

Source: George B. Muller, RPh • *Compounding Corner . Lacombe, Louisiana*

Methadone 20-mg/mL Chocolate/Raspberry Concentrate

For 100 mL

Rx

Methadone hydrochloride		*2.0 g*
Sodium chloride		*330 mg*
Sodium saccharin concentrate		*0.33 mL*
Stevia concentrate		*8.3 mL*
Flavor, "Bitter Stop"		*1.7 mL*
Flavor, raspberry anhydrous concentrate		*5.8 mL*
Flavor, chocolate		*1.7 mL*
Flavor, peppermint oil		*2 gtts*
Simple syrup		*42 mL*
Water, purified	*qs*	*100 mL*

Note: George Muller makes his own stevia and sodium saccharin concentrates. To receive those formulas, please contact George Muller by e-mail at the address provided in the accompanying article.

METHOD OF PREPARATION

1. Dissolve the methadone hydrochloride and the sodium chloride granules in 38 mL of the purified water and dissolve by stirring.
2. Add the simple syrup while stirring.
3. Add the flavors and sweeteners while stirring. 4. Add purified water to volume and mix well.

Methadone 20-mg Suppositories

For 20 each

Rx

Silica gel, micronized Food	0.4 g
color, yellow Fatty acid	0.02 g
base Methadone	42.4 g
hydrochloride	0.4 g

Note: This formula is calculated to fill a 2.3-g plastic disposable suppository mold to the 2-g line.

METHOD OF PREPARATION

1. Melt the fatty acid base at a temperature of 45° to 50°C on a hotplate.
2. Triturate the silica gel, the food color, and the methadone hydrochloride in a mortar to a smooth, even mixture so that the color is evenly distributed.
3. Sift the powders into the melted base.
4. Spin the mixture for 5 to 10 minutes with the heat off so that the melt can cool.
5. Allow the melt to thicken slightly and pour it into plastic disposable suppository molds.
6. Cool, trim, and package.

Methadone 20-mg/mL Pluronic Lecithin Organogel

For 100 mL

Rx

Methadone hydrochloride		2.0 g
Propylene glycol		1.5 mL
Lecithin/isopropyl palmitate solution		22 mL 3 3
Skin-So-Soft (Avon) Pluronic F-127		gtts
gel 20%	qs	100 mL

Note: George Muller prepares his own Pluronic 20% gel and lecithin/isopropyl palmitate liquid, both of which are now commercially available.

METHOD OF PREPARATION

1. Wet the methadone hydrochloride powder in a mortar with just enough propylene glycol to make a smooth, creamy paste.
2. Add the lecithin/isopropyl palmitate to the mortar and then add the Skin-So-Soft.
3. Mix briskly until the mixture "smacks."
4. Add sufficient cold Pluronic gel (20%) to mixture from step 2 to volume, using geometric dilution, and mix well, until a gel forms.
5. Pass the gel through an ointment mill or perform a syringe-to-syringe transfer to enhance micelle formation.
6. Withdraw the plunger from an empty syringe and backfill the syringe with the methadone Pluronic lecithin organogel (PLO).
7. Replace the plunger.
8. Cap the syringe.

Levorphanol 6-mg/mL Concentrate

For 100mL

Rx

Levorphanol tartrate		0.6
Flavor, "Bitter Stop"		g
Flavor, piiia colada concentrate		3 mL
Stevia concentrate		3 mL
Simple syrup		23 mL
Water, purified	qs	100 mL

METHOD OF PREPARATION

1. Add 63 ml, of purified water to a beaker, then add the levor phanol powder and mix until dissolved.
2. Add the syrup, then mix until uniform.
3. Add the sweeteners and flavors.
4. Add purified water to volume and mix well.