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Letter to the Editor

Concerns Voiced Over Methadone Results

To the Editor:

We read with concern the review article by Shalini Shah, MD, et al, "Methadone: Does Stigma Play a Role as a Barrier to Treatment of Chronic Pain?" published in Pain Physician (**2010; 13:289-293**). The article concludes that methadone is not just another opioid, but an "attractive" analgesic. Their message is clear: methadone is underutilized as an analgesic and that social stigma is a major culprit. The authors speculate that stigmatization of methadone, by patients, physicians, and the public may be a barrier to the use of this opioid as an analgesic.

As pain physicians based at a large, well-established, community-based, private practice and as public citizens, we have grave concerns about the conclusions of this article. The authors are experts at an internationally recognized pain management center. Their recommendations may be adopted by the general community and may be misinterpreted as an unintended consequence. We foresee situations where the onus will be on a pain physician to prescribe methadone per the request of the patient or significant others. If the doctor denies access to methadone, the patient may infer they are being denied due to sociological reasons—stigmatization or discrimination. This creates an opening for litigation based on discrimination or quality of care.

We contend that not only should methadone continue to be stigmatized both in the medical community and socially, but that its use for pain management should be further restricted and highly selective. However, the stigmatization we suggest is not for the reasons mentioned in the article. Simply put, methadone is an analgesic with significant and undisputed health risks not associated with other opioids. There is strong evidence that this medication may currently be used indiscriminately for reasons such as cost, and the notion of increased efficacy in treating neuropathic pain. There is also strong evidence that the increased use of methadone has led to a corresponding increase in deaths related to its use.

The authors miss an opportunity to discuss the enormous dangers of this drug. Methadone's distinctive metabolism and properties are associated with an increased risk of fatalities (1). Methadone, unlike other opioids, has a highly variable metabolism with a half life that ranges from 4-130 hours (2). The analgesic effect of methadone is shorter than would be expected based on the drug's half-life; prescribed dosing intervals in practice are shorter than the half-life—this has life-threatening consequences in individuals who metabolize the medication slowly. Drug accumulation develops and dose titration becomes difficult. Toxicity may develop within the first few weeks of treatment (3, 4).

The article, furthermore, minimizes the unique danger of methadone-associated cardiac conduction abnormalities, such as QT prolongation. Methadone has been conclusively shown to cause QT prolongation (6, 7). The authors discuss this issue in a way that implies that QT prolongation is an issue with parenteral administration of methadone. Parenteral use of methadone is exceedingly rare and QT prolongation leading to arrythmia is probably responsible for a number of oral methadone associated deaths.

The risks of overdose secondary to variable metabolism and QT prolongation have been deemed so serious that the Food and Drug Administration has issued a "black box" warning. In October 2006, the package instructions (PI) were revised to include additional "Black Box" warning information. The PI emphasizes that particular vigilance is necessary

during treatment initiation, during conversion from one opioid to another, and during dose titration. A high degree of opioid tolerance does not eliminate the possibility of methadone overdose. Deaths have occurred during methadone induction in opioid-naïve patients and during conversion from other opioids to methadone. Prescribers are urged to carefully read the prescribing instructions. Methadone HCl prescribing instructions were revised in October 2006. When starting opioid-naïve patients on oral methadone, the usual induction dose is 2.5 to 10 mg every 8-12 hours, slowly titrated to effect – 30 mg/d maximum. Vigilance is necessary to avoid overdosage, taking into account methadone's long elimination half-life. (The older prescribing instructions allowed induction doses up to 80 mg/d, which could be hazardous.)

The article also ignores one behavioral problem among chronic pain patients: patients are conditioned to take opioids frequently or "on demand." Methadone may be confused for opioids prescribed on an every 4 hours to every 6 hours basis. Patients may take methadone this frequently, despite admonition: this action compounds the already dangerous pharmacological properties of methadone 4-6 fold. Patients perceive prescription drugs to be inherently safer and may ignore warnings by physicians. This is the reality of community-based pain management. The authors missed an important opportunity to sternly warn of the dangers of this reality.

There has been a well-documented increase in the prescribing of all opioids over the last few decades. There has also been a well-documented parallel increase in the number of opioid-related deaths. Methadone far outstrips other opioids in terms of the ratio of specific opioid-related deaths to specific opioid prescriptions. From 2002 to 2007, the distribution of methadone by business categories associated with pain management such as pharmacies, hospitals, and practitioners nearly tripled, rising from 2.3 million grams to 6.5 million grams. From 1999 to 2006, the CDC reports that the number of poisoning deaths secondary to methadone increased almost sevenfold from 790 to 5,420 (8). In an evaluation by the Office of Analysis and Epidemiology, methadone-related deaths from 1999 to 2004 increased 390%, whereas the number of all poisoning deaths increased 54% (9).

Methadone is a uniquely dangerous analgesic. Okie, et al, in a recent New England Journal of Medicine article, echoed our concerns: "Methadone sales for chronic pain have increased partly in response to pressure from insurers and Medicaid programs, because the medication has been viewed as a cheaper and potentially less abusable alternative to other long-acting pain relievers. However, its very long half-life makes it tricky to manage and especially dangerous when combined with other drugs" (REFERENCE NEEDED).

Recently, the FDA has taken action against a number of opioid analgesics and is proposing a Risk Evaluation Mitigation Strategy for opioids, due to the rise in opioid-associated deaths.

Methadone should not be a front line drug for any type of pain or chosen for cost reasons, but utilized only as a last resort and only after all other alternatives have been exhausted. Special precautions must be in place before this drug is prescribed. Special precautions and careful monitoring protocols must be in place if this drug is prescribed. Methadone use should be limited to practitioners who understand the inherent risks of this drug. The purpose of a review article, unlike an editorial or letter to the editor, is to present a balanced appraisal of the literature. Special precautions must be in place before this drug is prescribed.

Scott E. Glaser, MD, DABIPP
President, Pain Specialists of Greater Chicago
Pain Specialists of Greater Chicago
7055 Highgrove Boulevard Suite 100
Burr Ridge, IL, 60527
E-mail: sglaser@painchicago.com

Ira J. Goodman, MD
Pain Specialists of Greater Chicago
7055 Highgrove Boulevard Suite 100
Burr Ridge, IL, 60527
E-mail: igoodman@painchicago.com

John P. Broadnax, MD
Pain Specialists of Greater Chicago
7055 Highgrove Boulevard Suite 100
Burr Ridge, IL, 60527
E-mail: jbroadnax@painchicago.com

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In Response to Concerns Voiced Over Methadone Results

The intention of the original article was to focus on stigma playing a role in the management of chronic pain, opioids, and methadone—not methadone alone. We suggested that in the 21st century, we ought to be focusing on the chemical properties, the mechanisms of actions, and adverse effects rather than social issues with medications. The role of NMDA receptors has been cited as being responsible for neuropathic pain in ample studies, as well as in chemical hyperalgesia. Methadone is the only unique synthetic morphine available that has a dual-receptor mechanism of action. It is a strong analgesic due to its effect as a μ-receptor antagonist, and effective on neuropathic pain and opioid-induced chemical hyperalgesia as an NMDA receptor antagonist. The purpose of our study was to point out stigma as a major barrier to usage, and not the drug itself. If the drug is not considered due to certain adverse effects and/or the lack of effect, it is an acceptable reason for not prescribing it, but stigma should not be the sole reason. Of course, every drug and every treatment have to be individualized after clearly understanding the risk- versus- benefit ratio to provide the best pain control to our patients. Dr. Glaser and his group's concerns are appropriate, but we should not judge the drug by its popular use by drug abusers. One of the author's experiences of using methadone for 14 years prompted this publication, anecdotally; it is not as bad as it is portrayed. Unfortunately, we do not have level I-II evidence that categorically helps us make the decisions. We have depended on mostly observational studies and data derived from patients who are on methadone maintenance to understand the effectiveness and safety of methadone rather than head-to-head comparisons of methadone with similar opioids. In fact, the lack of adequate studies in methadone usage may also be due ito ts stigma. The leading pharmaceutical companies are not interested in researching methadone because it will not be a blockbuster drug due to its stigma.

I agree with Dr. Glaser that deaths have occurred during methadone induction in opioid-naïve patients and during conversion from other opioids to methadone. But that's mostly due to our inadequate knowledge of the drug and/or lack of experience in using it. There is a learning curve for the use of methadone. Due to its irregular half life and potential for accumulation, these factors should be considered before starting a patient on methadone. The conversion factor also

varies from patient to patient, and also depends on the doses and chronicity of opioid usage. While converting from morphine to methadone, conversion factors vary from 5:1 to 10:1, and that is challenging and time consuming in the beginning only. Once the dose is identified, there is no need to escalate the dose, like it is required for all other opioids, as drug tolerance is an inherent property of all opioids except methadone. The "black-box" warning is for all opioids, not only for methadone. Methadone has never become popular as a "party" drug due to its lack of psychotropic effect. The addiction is psychological dependence on the medication, and it is least with methadone.

Even after the landmark article by Russell Portenoy and Kathy Foley from Memorial Sloan Kettering Cancer Center almost 2 decades ago, we have gone through many changes in the way we prescribe opioids. From writing very high doses and multiple opioids, we are moving away from writing at all! There is plenty of evidence in the literature that opioids are not as effective as we initially had expected. Opioids are not effective on neuropathic pain unless given in very high doses. The issue of chemical hyperalgesia secondary to high doses of opioids places a huge challenge for us. After we started using opioids, we learned that opioids are responsible for tolerance and chemical hyperalgesia. All 3 adverse effects are due to the poorly understood role of NMDA receptors. Now is the time to explore the anti-NMDA receptor activity of methadone.

I also agree with Dr. Glaser regarding conditioned behavior of chronic pain patients. But that is due mainly to our style of practice. We have not clearly understood the underlying mechanism of acute non-chronic exacerbation of non-malignant pain with any identifiable causes. I believe chronic pain is on-going process and those patients should be on longer acting medications. They should not require short acting medications to use for break-through. The large amount of short-acting medications encourages potential abuse and diversion of these medications. Studies have shown that the highest prescription abuse is with Percocet and Vicodin. Methadone is not a short acting medication and should not be used frequently for break-through pain, otherwise, as Dr. Glaser pointed out, it will accumulate and cause overdose effects. Patients do perceive prescription drugs to be inherently safer and it is the responsibility of physicians to educate patients.

We cannot agree more with Dr. Glaser that there has been a well-documented increase in prescriptions of all opioids and occur parallel increase in the number of opioid-related deaths over the last few decades. Methadone-related deaths occur in those patients who are in methadone maintenance programs, and are not a clean sample of patients. Those patients who abuse illicit drugs like heroin also are known to abuse other drugs like cocaine and amphetamines which are inherently sympathomimetic drugs, and those deaths cannot be attributed to methadone. Unfortunately, there are no industry supported dinners or speaker's programs for methadone that will stimulate us to learn more about the medication. It is our responsibility to learn the efficacy and safety of the medication like we have learned for intravenous Pentothal and Propofol, and not close the doors from learning and using solely due to stigma.

If cost cutting is the primary reason for prescribing, then methadone should never be used for any pain type; however, it is an added bonus that such an efficacious drug is also generically available and economical to its prescribed patients.

We want to thank Dr. Glaser and his group for reading the article and expressing their concerns. This is exactly what we had expected. We should not close the doors to explore all the properties of the drug, especially as we do not have many options available as NMDA receptor antagonists. Ketamine is gaining popularity, but it is mainly for OR use, and limited by its severe emergence delirium adverse effects. Ketamine, being a sympathomimetic drug, poses life-threatening complications if used in patients with coronary artery disease. We appreciate the discussion to our article and invite any further responses.

Shalini Shah, MD
Department of Anesthesiology and Pain Medicine
Weill Cornell Medical College
525 E 68th St Box 124
Room M 305
New York, NY 10021
E-mail: shs9096@nyp.org

Sudhir Diwan, MD
Dept Anesthesiology and Pain Medicine
Weill Cornell Medical College
New York, NY 10021