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W–15: A NEW, POTENTIAL OPIOID OF ABUSE

To the Editor:

In recent years, epidemiological and clinical information have highlighted a significant increase in the use of new psychoactive substances around the world.[1] These compounds, sold in smart shops, research chemical stores and online, include both synthetic molecules and plant derivatives mimicking the psychotropic effects of traditional and illicit drugs of abuse.[1]

In 2013, in addition to many new synthetic cannabinoids, cathinones, phenethylamines and arylalkylamines, five synthetic opioids have been officially notified for the first time to the European Monitoring Centre For Drugs And Drug Addiction (EMCDDA) via the Early Warning System (EWS).[1] Among them, W-15, IUPAC name 4-chloro-N-[1-(2-phenylethyl)piperidin-2-ylidene]-benzenesulfonamide, appears to be the less known and the most potentially dangerous. W-15 is an analgesic opioid chemically unrelated to other opioid medicines.

It was synthesized in 1981 by Knaus, Warren and Ondrus and patented in the 1984.[2] Knaus and colleagues synthesized numerous piperidylidene-2-sulfon(cyan)amide derivatives with analgesic agonist or analgesic agonist-antagonist activity.[2] Starting to the general chemical structure (Figure 1), they prepared various compounds wherein R1, R2, R3 and R4 groups were replaced with various different chemical substituents.

In particular, W-15 was obtained adding the C6H5(CH2)2 and SO2-C6H4-4-Cl group in R1 and R2 position, respectively (Figure 2). Analgesic activity was investigated using the phenylquinone writhing assay in male Swiss albino mice. This test showed that W-15 exerted an analgesic effect 5.4 times more potent than that of morphine.[2] Specifically, five male Swiss albino mice weighing 18-22 g were used to test the analgesic activity of W-15 and its analogues. The test compound, suspended in a solution of physiological saline and Tween 80™ surfactant, was administered subcutaneously, and 30 minutes later all mice received intraperitoneally a 0.03 percent phenyl-p-benzoquinone solution in a volume of 0.1 mL/10 g of body weight. This test showed that 0.007 mg/kg of W-15 caused a reduction in the total number of writhes exhibited by mice greater than 50 percent. As a comparison, the same result was

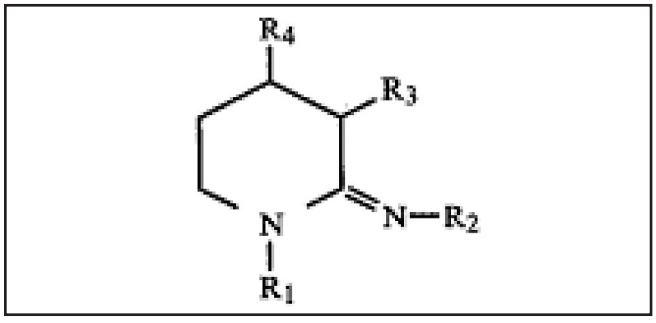

Figure 1. Piperidylidene-2-sulfon(cyan)amide derivatives general chemical structure.

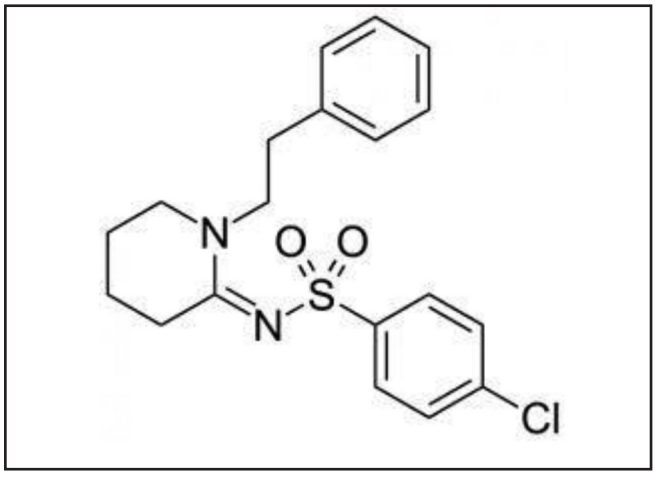

Figure 2. W-15: C6H5(CH2)2 and SO2-C6H4-4-Cl groups are R1 and R2 substituents, respectively.

produced by 0.038 mg/kg of morphine, 50.0 mg/kg of aspirin and 56.0 mg/kg of dextropropoxyphene.[2]

To date, W-15 is sold in online research chemical stores and it is labelled as a "potent analgesic opioid not for human consumption." However, self experiences reported within the drug forums suggest a certain popularity among drug users.[3] Furthermore, other potent analgesic opioids belonging to the "W" family such as W-18 are available in online research chemical stores increasing the risk of a global spread among opioid derivatives users.[4]

In conclusion, W-15 is a little-known substance and no study has evaluated its pharmacological and toxicological properties in humans. Preclinical investigations performed using the phenylquinone writhing test have demonstrated that this opioid exerts an analgesic activity more potent than that of morphine. It is available in online research chemical stores and consequently it is easily accessible to a large public. Moreover, W-15 is considered a legal

substance in many countries and this fact could encourage opioid derivatives users to experience its consumption. W-15 possesses the characteristics to become a new global public health concern and the "W" family could become a novel generation of potent and dangerous analgesic opioids of abuse. International cooperation is of great importance in order to monitor and prevent the spread of W-15 and its analogues among drug users.

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IS THERE A PARADOX BETWEEN OPIOID–PRESCRIBING BY PHYSICIANS AND NEGATIVE ON–LINE RATINGS BY PATIENTS?

To the Editor:

Thank you for giving us the opportunity to discuss a frequently encountered dilemma during chronic pain management, ie, opioid prescribing by physicians and negative online ratings by patients. As we all know, chronic pain is pervasive and costly. Based on a recent report published by the Institute of Medicine (IOM), it is estimated that chronic pain affects 116 million American adults—more than the total affected by heart disease, cancer, and diabetes combined. Pain also costs the nation up to $635 billion each year in medical treatment and lost productivity.[1] In light of the pervasion, cost, and consequence of poorly controlled pain, IOM calls for a concerted effort to transform how the public, policy makers, and health care providers view this situation, ie, a "cultural transformation" in how Americans understand and approach pain management and prevention.

Opioids/opiates have been used for centuries and remain the most potent and reliable analgesic agents.[2] While there is no debate over the short term use of opioids, their use for chronic non-malignant pain is controversial and there is growing reluctance among some physicians to prescribe them.[3] The problem is the most powerful opioid analgesics are also the most liable to cause misuse, abuse, addiction, and diversion. Should opioids be used in patients with non-malignant chronic pain? Or, will patients with non-malignant chronic pain be harmed if opioid analgesics are withheld for concerns of misuse, abuse, addiction, or diversion?

Despite the lack of convincing data for long term efficacy and the growing problem of prescription abuse, many physicians prescribe opioid analgesics for patients with chronic nonmalignant pain. The reasons are complex, but many believe that it is unconscionable to withhold adequate treatment from any patient complaining of severe pain, whatever the cause, especially when alternative treatment fails.

In 2009, the American Pain Society and the American Academy of Pain Medicine issued joint guidelines recommending the judicious use of opioid analgesics when chronic noncancer pain is moderate or severe, when it has an adverse effect on function or quality of life, and when a careful risk-benefit assessment indicates a likely net benefit.[4]

More recently, in the March 2013 issue of *The American Journal of Medicine*, de Leon-Casasola opined that "For older adult patients at higher risk for NSAID-related adverse effects, such as those who have gastrointestinal or cardiovascular disease, diabetes mellitus, or who are taking low-dose aspirin, opioids are recommended instead. Opioids may also be an appropriate option for patients with neuropathic pain who have not achieved adequate analgesia from maximum doses of first- and second-line anti-neuropathic agents."[5]

Indeed, in the context of expanded pain care, opioid consumption levels have tripled globally since 1990. In the US, the total amount of opioids

prescribed, measured in morphine-equivalent doses (MEDs), increased more than 600 percent between 1997 and 2007. More than 200 million opioid prescriptions are now written every year.[6] With the increased availability of opioids, diversion of these medications to nonmedical use has also increased. In 2010, more than 12 million individuals in the United States were estimated to have used opioid analgesics nonmedically and approximately 1.8 million people had abused or become dependent on these drugs, and approximately 16,000 overdose deaths were attributed to prescription opioids.[7] The rise in overdose deaths has led to media headlines and increased social concern. This, in turn, has provoked law enforcement efforts to disrupt and punish diversion. While the effectiveness of law enforcement approaches to this problem are debatable, these well-meaning efforts further complicate physician decisions. In addition to concerns about contributing to opioid addiction and diversion, many fear investigation, censure, or even arrest for prescribing these drugs. Law enforcement efforts to stem illegal diversion of prescription medications have very likely shifted the balance in the medical community back toward under-prescribing opiates. At this point it is unclear whether the increased fear of creating an addict or of being investigated by law enforcement has hurt more individuals because their pain relief is inadequate or has helped more by reducing access to a potentially addictive substance.[3]

Apparently, the use of prescription opioids for the treatment of pain is challenging and complex. There exists a prevailing tendency towards inappropriate patterns of under prescribing (because of fear of adverse effects and addiction) or overprescribing (because of failure to select properly or frustration over a poor therapeutic response). These practice patterns are especially prevalent in the management of patients with chronic noncancer pain and have resulted in or contributed to unnecessary patient suffering from inadequately treated pain and increasing rates of opioid abuse, addiction, diversion, and overdose.[8]

Indeed, physicians, who prescribe opioid analgesics to treat chronic pain, are fully aware of the danger facing them nowadays, during an era flooded with unpredictable changes in health care policies. Pain management has become so over-regulated by state and federal agencies, that one misstep in either direction of the provider may result in fines, loss of licenses, or even jail time. Inappropriate opioid analgesic prescribing for pain is now defined as the non-prescribing, inadequate prescribing, excessive prescribing, or continued prescribing despite evidence of ineffectiveness.[9] Lawyers these days have the easiest scenario to sue physicians, either for under treating pain when prescribing too little pain medication or over treating pain when the prescribed drugs appear to be too much.[8]

Over the past a few years, on-line physician rating websites have proliferated at an alarming speed, thanks to the internet. Although these for-profit websites were created to facilitate transparency, euphemistically described as physician ratings, they have actually become doctor-bashing websites.[10] Historically, if a patient was unhappy with care, he or she could tell his or her friends and family. The criticism was limited to a small circle of people. With the Internet, if a patient is dissatisfied, he or she needs do little more than access a growing number of Internet physician rating sites. Such criticism can be rendered anonymously. The posts are disseminated worldwide, and once posted, they rarely come down. While physicians are bound by state confidentiality laws and the Health Insurance Portability and Accountability Act (HIPAA) to hold their tongues, physicians are forbidden from defending against reputational assaults by posting the medical record as a correction.[10]

We speculate that physicians, who manage chronic pain, are more prone to negative on-line ratings for the following reasons:

- Treating patients with chronic pain is a very challenging task. The American Academy of Pain Medicine estimates that four of 10 patients with moderate-to-severe pain do not get adequate relief from their analgesics, while nearly one of four patients change health care professionals three times because of perceptions of suboptimal pain care.[5] Every clinician who treats patients with chronic pain routinely faces difficult dilemmas. Treatment approaches, even if multidisciplinary, are often unsuccessful. For persistent pain sufferers, the search for results is met with an increasing sense of failure, dissatisfaction, and frustration. In this setting, on-line physician ratings can be an avenue for a patient to vent frustration.

- The regulation of controlled substances has

a "chilling effect" on the prescribing and dispensing of opioid analgesics.[8] Several surveys have shown that the fear of being scrutinized by regulatory or law enforcement agencies compels many physicians to prescribe fewer opioids. Many physicians are particularly reluctant to prescribe opioids for their pain patients who do not have cancer. The undesirable effect of the "chilling effect" is the under-treatment of pain. Few are aware of the massive healthcare problem of under-treatment of pain. For example, a study in the Journal of the American Medical Association concluded that 40 percent of the 2.2 million nursing home residents in this country live with "moderate" to "excruciating" pain daily, which is not treated for as long as six months after being reported.[11] Many studies corroborate such under-treatment across society, for young and old alike, and the negative impact on society of under-treatment of pain on quality of life, work productivity, general health status, and health care costs.

- Because of the immensity of the burden of chronic pain, there is a critical need for family physicians and general practitioners to manage patients with chronic pain. Otherwise, in order to manage all Americans with persistent pain, each and every practicing pain specialist in the United States would have to treat approximately 21,000 patients.[5] This projected statistic underscores the need for multidisciplinary cooperation in the treatment of chronic pain, with joint efforts by primary care physicians as well as other health care professionals. Yet, the fear of being scrutinized by DEA or law enforcement agencies and censure by a state medical board, brought about by the "chilling effect" from DEA and regulatory agencies may lead to less opioid prescribing by primary care physicians. Many established, chronic pain patients, managed by primary care physicians, will be referred out to pain specialists for continuation of opioid therapy. The extra patient load, added to an already busy, fully stretched clinic schedule, is prone to be problematic. When this happens, the allocated patient-physician interaction time is shortened, wait-time prolonged, etc., simply because there are too many patients on schedule needing to be seen.

- The most important factor, we believe, is the change of the medical practice model, from the traditional style, when physicians used to be the powerful and chief decision maker, to the current format of shared decision making, where all of the alternative treatments and outcomes are explained to the patient, and the patient becomes the chief decision maker, while the physician provides the guidance. In a pain practice that uses opioid analgesia for chronic pain management, conflict between the patient's expectation/demand and the physician's judgment/decision are frequently encountered. When there is a disagreement between the patient and the physician regarding the opioid therapy, for reasons such as repeated aberrant drug behavior, inconsistent urine drug testing, multiple illicit drugs detected in urine testing, noncompliance with opioid therapy, no functional improvement while on opioid therapy, sharing opioid medications with others, etc., the shared decision making model will create major problems as the patient may still insist on continuing opioid therapy, while the treating physician will (should) terminate (taper off) opioid therapy. The patient's "satisfaction", in this setting, should be avoided. Health care organizations frequently utilize patient satisfaction ratings as an integral part of marketing and benchmarking of services.[12] This can be problematic when it comes to opioid pain treatment: clinicians may feel threatened into prescribing in order to meet the satisfaction metrics by which they and their practices are judged. Here, prescribing opioids to drive up patient satisfaction metrics is not justified.[12] This is especially true in the setting of physicians prescribing opioid analgesic for chronic non-cancer pain, because what we use are not only potent analgesics but also compounds that are potentially liable for abuse, misuse, addiction, and diversion. There will be situations that opioid treatment is not suitable and should be denied, even when the patient

> demands it, or claims satisfaction. Denying opioids in some cases is ethically justified. However, the patient may easily turn to numerous on-line physician rating sites to vent his "dissatisfaction".

After all, is it truly fair or transparent? Or is it a valid thing to do—to rate a physician's care like merchandise, such as a microwave or a barbecue grill?

We think not. First, the quality of medical care is composed of many elements, but online rating by patients focuses only on those they are able to give opinions on, and excludes those they are not.[13] In medicine, the concept of good quality service should be the best health outcomes at the lowest cost. While it is possible that a customer can judge how good the food is in a restaurant, it is almost impossible for a patient to judge whether a doctor has conducted the best possible medical care for his/her medical condition. Patient satisfaction instruments have many limitations, including lack of psychometric standards, the poor reliability and validity of surveys, and discriminatory assessment.[13] Second, most of the rating sites have, at most, only a handful of posts. The size of such a sample, in comparing to the number of patients that any given physician takes care of, lacks any statistical significance. In addition, on-line physician ratings are flawed with opinion bias. Patients are more likely to rate the doctor online when their own requests are not met by the doctor.[13] Furthermore, there is lack of accountability or quality control as these on-line postings are often done anonymously. It is impossible to tell if the rater is a patient or someone posing as a patient, such as a disgruntled employee, an ex-spouse, or a competitor. Third, those numerous for-profit physician on-line rating sites not only can harm physicians, but patients, or even our society. The most important asset of a physician, i.e., his or her professional reputation, can be easily ruined by such postings, even if none of them are grounded in fact; once posted in cyberspace, they are accessible 24/7 to anyone with minimal computer literacy, and the messages do not come down. The damage to a physician's profession can be extensive.[10]

In a recent article titled "Why Doctors Prescribe Opioids to Known Opioid Abusers," by Dr. A. Lembke, published in the Oct. issue of *New England Journal of Medicine,*[14] she opined: "In many instances, doctors are fully aware that their patients are abusing these medications or diverting them to others for nonmedical use, but they prescribe them anyway."; "Doctors' clinical skills may also be evaluated on for-profit doctor-grading websites for the world to see. Doctors who refuse to prescribe opioids to certain patients out of concern for abuse are likely to get a poor rating from those patients"; "Health care providers have become de facto hostages of these patients, yet the ultimate victims are the patients themselves, who are not getting the treatment for addiction they need and deserve." The same concern is shared by many physicians across the country. For example, Dr. Zgierska and colleagues published an article, titled "Patient Satisfaction, Prescription Drug Abuse, and Potential Unintended Consequences,"[15] in which the authors opined: "They may paradoxically promote prescribing of opioids and other addictive medications."; "Physicians who comply with unreasonable requests may find themselves in the role of "customer service" providers rather than medical professionals or healers; physicians who do not comply with patient requests may be the recipients of poor ratings on patient satisfaction scores, possibly resulting in emotional, financial, and professional penalties. These issues may be inadvertent but powerful disincentives for physicians to provide medically correct care and may contribute to the erosion of trust needed in a healthy patient-physician relationship".

We speculate that the irresponsible and reluctant opioid prescribing to "please" patients, for concern of receiving negative ratings, may have played a role in causing the "prescription opioid endemic" that we are facing today. We wonder if our viewpoint can be shared with other viewers and we would love to receive some feedback or comments from other colleagues.

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A CASE OF PHYSICAL AND PSYCHOLOGICAL DEPENDENCE ON BUTORPHANOL

To the editor:

Opioids have been used for postoperative pain management for a long time and are a standard in treatment[1] and have a high potential for abuse and dependence. Risk of dependence has been seen in patients prescribed opioids for pain management, which is 0 to 8 percent in patients with cancer pain and 0 to 50 percent in those with non-cancer pain.[2]

We report here a case of physical as well as psychological dependence on butorphanol in a young adult after being prescribed injectable opioid analgesic for post-operative analgesia.

Case history:

A 29-year old male with a fractured tibia was prescribed injection pentazocine in the hospital after operative procedure for pain relief. At discharge, pentazocine was stopped. However, the patient kept getting the drug from some source whenever he felt any pain at the fracture site. Patient learned about a similar medication in a nasal spray (butorphanol) preparation and its ease of use. He started using the butorphanol nasal spray (10mg/ml, 2.5 ml bottle) from a friend and started using it instead. He noticed a feeling of pain relief as well as calmness after taking the dose. His use increased from one puff (~1 mg) every six to eight hours, with one bottle lasting roughly four to five days to one bottle of butorphanol (25 mg) every alternate day. He could not afford the spray on his income so he started borrowing money and incurred a large debt and decided to stop using the spray and abstained from it. He presented to the ER the next day with restlessness, loose stools, abdominal pain, and watering from eyes.

The patient did not have any concurrent substance abuse or dependence, past or family history of psychiatric illness, significant medical or surgical illness. On examination, patient had tachycardia (118/min), hypertension (142/98 mm of Hg) and flushed face. General examination also showed profuse lacrimation and rhinorrhea. Apart from fine tremors, systemic examination was within normal limits. Mental status examination showed a well groomed, fidgety and restless male with ill sustained

attention. Mood was anxious with congruent affect. Thoughts contained preoccupation with the physical symptoms and severity of withdrawal was prominent. Intense craving for the drug was present. Patient denied delusions or abnormal perceptions. He was oriented to time, place and person.

Patient was diagnosed as opioid dependent with physiologicalcal dependence as per DSM-IV TR criteria and was admitted. Routine investigations such as complete blood count, liver function tests, electrocardiogram and chest X-ray were done all of which were within normal limits. Patient was managed on lorazepam 6 to 9 mg (with provision for intravenous lorazepam as per need) in divided doses (with regular monitoring of vital parameters, SpO_2 and pupils), paracetamol 500 mg tds and diphenoxylate 2 mg bid. Patient was assessed regularly for vital functions, mental status, pupils and vegetative functions.

Patient showed an uneventful yet prolonged withdrawal with complete remission of withdrawal symptoms on 10th day. Lorazepam and other medications were slowly tapered down and stopped before discharge. Patient was started on tablet naltrexone 50 mg on 12th day from abstinence and was informed about the need for regular follow-up.

Discussion

Butorphanol is a synthetic opioid analgesic with a κ agonist and a partial agonist action on μ receptors.[3] It is one of the few opioids which is available as an intranasal spray and has low toxicity and a low potential for abuse. The dependence potential for trans-nasal and parentral preparation of butorphanol was thought to be equal.[5] However there has been a 6 to 24 percent increase in dependence rates among all adverse drug reactions after the drug was launched in nasal spray formulation.[4] Another aspect of butorphanol is its partial μ receptor agonist action. In animal models, butorphanol has been hypothesized to precipitate withdrawal if given concurrently with other opioid compounds,[4] a finding observed in certain reports.[6] Thus a prescription of butorphanol with another high efficacy opiate warrants caution and monitoring for possibility of an exacerbated withdrawal from the opiate.

Despite the proposed rise in butorphanol dependence after the nasal-spray launch, only a small number of scientific literatures describing butorphanol dependence exist.[7,8] The case also highlights the possibility of an emerging trend of butorphanol abuse/dependence and the necessity for better safeguards and legal statutes against availability of opioid analgesics without proper monitoring.

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