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Methadone Analgesia for Persistent Pain: Safety and Toxicity Considerations

Frederick W. Burgess

E. Pawasauskas
University of Rhode Island, jaynep@uri.edu

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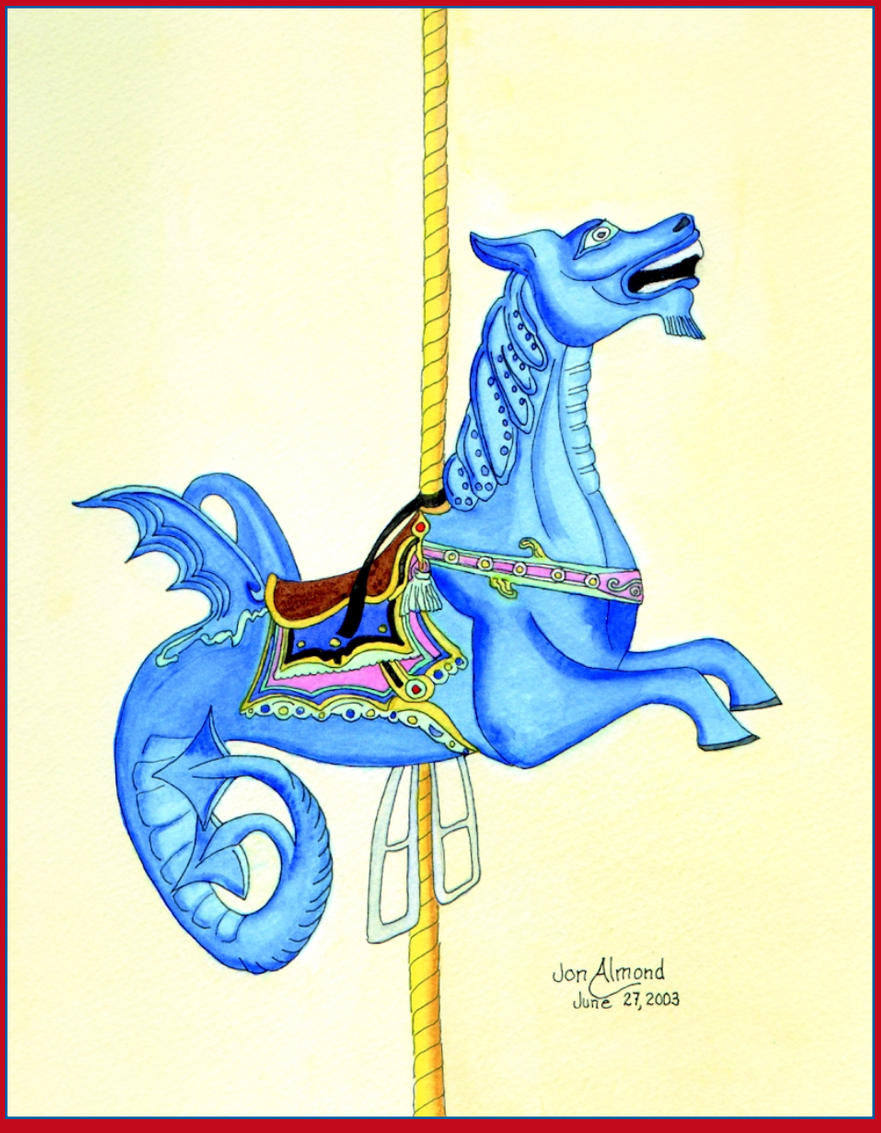

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COMMENTARIES

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SPECIAL ISSUE: Pain Management
Guest Editor: Frederick W. Burgess, MD, PhD

COLUMNS

Correction: The article title, "Obesity Hyperventilation Syndrome in the Differential Diagnosis of a Pulmonary Mass," by RF Lain, C Superczynski and RS Crausman, *Medicine & Health/Rhode Island* June 1997;80:193-5 is incorrect. The correct word is "Hypoventilation."

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Commentaries

Electronic Medical Records

Almost every op-ed piece on medical care in America praises electronic medical records. They are never lost. They can be sent to any office in the world in a split second. The records can be faxed, often directly from the computer. The patient can get a copy of the record in a flash. The doctor can field questions from the patient or another doctor with the virtual chart available for review in a few seconds. Some charts may be accessed from sites distant from the office so on-call doctors can renew medicines and answer queries even when they don't know the patient. Sounds great, and to some extent it is. But have you visited a doctor who uses computer records?

My **primary care provider (PCP)** uses the computer to enter data, and now, so do I. The first obvious drawback is that it requires the doctor to appear rude. As the patient speaks I have to enter information via the keyboard. For a new patient I have go through a vast array of alphabetized possible illnesses to click on whatever disorder they may have had to complete the medical history. When the illness is not on the list, entering it takes more effort. It is a time consuming and annoying process.

When my own PCP started using the computer, he now longer faced me as we talked. Half his concentration was on the keyboard, half on me. Previously we'd chat and he'd casually make entries in the chart, by hand. Since "if it isn't charted it didn't happen," he's entering everything as quickly as possible.

I tolerate my own misspellings because I don't have the time or patience to review what I've written. If the patient remembers something relevant to a preceding topic I have to backtrack and enter that bit of data. It has a subtle influence to reduce pursuit of further information. Worse still, because it takes longer than a handwritten note, there is now even less time for a visit than there used to be. And it is truly amazing how many of my patients say, "Oh, by the way…" presenting me with a major problem to discuss, after I've closed the program.

When I want to review the last visit, I have to close down my current screen and flip up the previous one. I can minimize the current screen but it's not like turning pages. Then I go back to the current visit; but if I need to check another fact about the previous visit, I have to minimize or save the current note and recheck the old one. It's not nearly as efficient as flipping through the chart. When I want to check a lab, or an MRI, I have to close the current note and hunt for the data, read it, close the screen, open the new note, and hope that I can remember exactly what I want to include in the current note. Sounds challenging? Not really, but quite annoying. And the software program that I use doesn't accept outside lab or imaging reports so that the labs are entered in a different software program. I have to not only minimize my current note, but I have to open a whole new program, find the patient and then the data set that I need. It's like comparison shopping on the internet, first checking a price at one site then at another, except in the office there are major time constraints.

There's no doubt that I don't have to worry about losing charts, that is, unless the receptionist mistypes the patient's name. In the old days, the charts were kept alphabetically, so the chart on "Bailey" misspelled as "Baily" was easily found, whereas the computer generates the list of everyone named Bailey, but Baily won't appear. Now that I've had this problem a few times, I've learned to reduce the number of letters I use, so that "Bail" will include all names beginning with those four letters. If I can't find "bailey" then I try Bail, or Bal. If there are a lot of names beginning with those letters, I'm in trouble. An entry of "Boley" may remain unknown forever.

My chart notes have taken a nose dive in quality. I used to dictate my notes and prided myself on their completeness. No longer. Now the history contains a bunch of click items, "patient admits history of hypertension, valvular disease, GERD and eye problems." The click method is important for billing.

I get electronic notes from other doctors that seem to have been generated by secretaries who entered data from extensive forms filled in by the patient. They have filled out forms endorsing: dizziness, low back pain, blurred vision, headaches, gastritis, rashes, and a host of other symptoms, entirely irrelevant to why the patient saw the doctor. Sometimes I can't even figure out why the patient saw that doctor, what the doctor found or what happened at the visit. Completeness to the point of irrelevancy.

I can't seriously say that computerized records are bad. Overall they probably are good. In the hospital charts are never lost. Lab values are always available. Doctors' notes are always legible. There is less chance for errors. Alerts on labs or drug interactions can be made automatic to lessen their chances of being overlooked. But they are not an unalloyed good. They undoubtedly save money, especially if notes are no longer dictated. Dictated notes can, of course, be computerized, but there is a tendency to try to make everything as click-driven as possible.

In the future, when all records are computer based, hopefully simplified and universal in nature, the payoff, in which all patients can carry the important parts of their records on a computer chip embedded in a medical record plastic card, will be worth it. Until we get there, electronic records are, in my mind, a mixed blessing. They represent the "regression toward the mean," a method which reduces the quality of the best, improving to some degree the quality of the worst, but primarily making all notes mediocre but more readily available and, perhaps most importantly, readily available to those who really count in our medical world, the insurance companies, the ones who pay the bills.

In the United States, where some elected officials view George Orwell's *1984* as a template rather than a nightmare, the concept of a national repository of medical information poses a great threat to our privacy.

– Joseph H. Friedman, MD

Disclosure of Financial Interests

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The Decline and Fall of the Red Tomato

"Do you really want to purchase these tomatoes?", whispered the checkout woman at the supermarket. She stared at the tomatoes for a moment as though they were packets of lethal anthrax and then exclaimed, "Last week it was poisoned tomatoes; a month ago, contaminated eggs; and don't forget such things as avian flu and that sickness from the Nile River. Life is getting scarier."

I dutifully paid for my groceries, including the lush tomatoes, tacitly agreed with the employee about the sundry hazards of urban existence and reflected upon her litany of focused fears. To what extent were her anxieties justified? To what degree were they part of a nonspecific [and possibly counterproductive] cloud of fear that so many experience in a world of expanding complexity?

On June 7, 2008, the US **Food & Drug Administration (FDA)** warned American consumers that an outbreak of Salmonella infection "had been linked to consumption of some raw red plum, red Roma, round red tomatoes and products containing these raw tomatoes." By early summer of 2008, the FDA had substantiated 887 cases of salmonella enteritis, inferentially associated with the consumption of certain varieties of tomato. The outbreak centered particularly in Texas and New Mexico. [Salmonella enteritis, it should be pointed out, is not that rare a clinical phenomenon. In an average year, the United States witnesses about 1.4 million cases. Still, the government publicized this outbreak since they thought that its source was readily identified.]

What is salmonella? It is the name given to a genus of biologically related bacteria [some innocuous, some dangerous] that inhabit the gastrointestinal tracts of domesticated birds and animals as well as certain reptiles such as turtles.

Two American scientists, Theobald Smith [1859 – 1934,] a physician and experimental pathologist, and Daniel Elmer Salmon [1850 – 1914], a veterinarian who had founded the governmental Bureau of Animal Industry, a precursor to the FDA, were jointly studying the causes of a sometimes lethal cholera-like disease in domesticated swine. In 1885 they isolated a specific bacterium which was later named Salmonella. Since then, other members of the Salmonella genus have been shown to cause typhoid fever, paratyphoid fever; and one species of Salmonella, *Salmonella enteriditis*, is the major cause of food poisoning in this nation and abroad. The interpersonal relationship between Salmon and Smith is both odd and contradictory. On the one hand, their collaborative investigations yielded much scientific insight into the nature of enteric infection and the development of antibodies to these illnesses; on the other hand, there was much continuing enmity, even outright antagonism, between the two.

Salmonella food poisoning [enteritis] causes an acute illness characterized by an incubational interval of 12 to 18 hours, moderate fever, abdominal distress, diarrhea [usually nonbloody] and in most cases recovery within four or five days. The self-limiting illness tends to be more serious in three categories of vulnerable humans: the nursing home elderly, the premature infants, and those with temporary or enduring immune deficiencies such as those suffering from HIV infections or those undergoing extensive radiation therapy.

The germs causing salmonella food-poisoning, historically, have clustered in the intestinal tracts of domesticated chickens; accordingly, the great majority of salmonella food-poisoning cases occur in those eating raw or undercooked eggs. These bacteria often contaminate the interior of the egg prior to its being encased by the shell; and therefore sterilizing the chicken-shell may not affect the integrity of the Salmonella bacteria harbored within the egg. Adequate cooking of eggs, then, remains the most dependable means of preventing Salmonella food-poisoning.

More recent epidemiological studies of recent cases of Salmonella food poisoning now cast doubt that tomatoes were the sole, or even principal, source of the outbreak. Given the complexities of farming, storage, distribution and retailing of a vegetable such as the tomato, the actual point of intimate contact between the pathogen and the vegetable carrier may never be determined to anyone's critical satisfaction.

From whence came the tomato? It is one of many New World contributions to the cuisines of Europe, Africa and Asia. Some think that it originated in the highlands of Peru; but most agronomists now believe that its deliberate cultivation was begun by Central American Aztecs. Indeed, the Aztec word for the vegetable is *xitomatl*.

Cortez conquered the city of Tenochtitlan in 1521 and the tomato plant soon found its way east across the Atlantic, first as an ornamental plant. By 1544 tomatoes entered into the southern Italian cuisine, called *pomi d'oro* [golden apples]. The transplanted tomatoes of the 16th Century are now presumed to have been the yellow cultivar, hence the name "golden."

In France the tomato was called *pomme d'amour* or love apples because of tomato's alleged aphrodisiac quality. In England as well as the northern nations of Europe, however, the tomato was viewed as a poisonous plant [perhaps anticipating the science-fiction cinematic thriller of the 1960s, "Attack of the Killer Tomatoes."] Not until the 19th Century were tomatoes incorporated in the general diet of Germanic and English-speaking nations.

The average American, through his diet of pizza, salsa, tortillas, tomato soup, garden salads, ketchup and sundry other culinary exploitations of the tomato, now happily consumes over 38 pounds of tomato per year.

– Stanley M. Aronson, MD

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Stanley M. Aronson, MD, has no financial interests to disclose.

Correspondence

e-mail: SMAMD@cox.net

Opioid Therapy and Prescription Drug Diversion

Frederick W. Burgess, MD, PhD, and Jayne Pawasauskas, Pharm D, BCPS

Physician and patient attitudes toward pain treatment have fluctuated dramatically in recent years, influenced by opposing concerns regarding humanitarian considerations and the potential abuse of our most effective analgesic class, the opioids. Unfortunately, the widespread abuse of opioid preparations, with its social consequences, led to today's close government restriction.[1] Admittedly, opioid medications, both illicit and prescribed, are abused, but when prescribed for appropriate medical indications, the medications can improve our patients' physical and emotional well-being.[2] Fortunately, many barriers to pain treatment have diminished over the past 20 years. In addition, we have more effective delivery systems and dose forms. Consequently, we have witnessed a dramatic increase in opioid prescribing for all forms of pain, including acute, cancer, and other persistent pain conditions.[2,3] This greater willingness to treat pain has been marked by an increase in opioid production and distribution by the pharmaceutical industry, which has embraced pain treatment as a growth market.[4] While all government agencies and healthcare experts regard appropriate pain treatment as good medical practice, many question whether the pendulum has swung a bit too far in favor of liberal or even excessive opioid prescribing by some practitioners. Despite this notable escalation in opioid prescribing and consumption throughout the US, inadequate pain treatment and inequalities in patient treatment persist.[5,6]

Coinciding with the greater availability of prescription opioids, there has been a parallel increase in the abuse of prescription opioids, and in overdose deaths throughout the US.[7] Substance abuse involving heroin and stimulants, while widespread, generally is associated with major metropolitan areas. Over the past ten years, there has been a marked upsurge in accidental overdose deaths and emergency unit admissions involving prescription opioid overdose in previously less affected rural communities in states such as Maine, West Virginia and Vermont. (Table 1) In many of these communities, illicit opioids had been much less available, but with the dramatic increase in opioid prescribing for pain, many prescription opioids are being diverted for illicit consumption.[7,8] According to the most recent DEA data, hydrocodone, oxycodone, and methadone are the predominant opioids contributing to accidental opioid overdose deaths, exceeding those reported for heroin and cocaine. Several factors have contributed to this escalation in prescription drug abuse; e.g., greater availability of high-dose sustained release opioid formulations, the purity and perceived safety of prescription medication, and the ease of access to these medications from their parents' medicine cabinet by college age adults. The majority of opioid-related deaths involve multiple central nervous system depressants, including alcohol and benzodiazepines, in addition to stimulants such as methamphetamine, and cocaine.[8] Hydrocodone appears to be the predominant opioid associated with prescription opioid abuse, probably reflecting its' greater availability as the most prescribed opioid. Oxycodone follows as a close second, with methadone a more distant third.[7] However, in considering accidental overdose deaths, methadone has proven much more lethal, despite the fact that it is prescribed an order of magnitude less than oxycodone and hydrocodone, reflecting methadone's unique pharmacology, which will be discussed in a subsequent article in this issue. Methadone is commonly sought by opioid addicts as a means to stave off withdrawal symptoms between episodes of abuse or dismissal from an opioid treatment facility, fostering a surprisingly high street-value.[9]

It is impossible to completely separate the analgesic properties and the abuse liability of the opioid drugs. Efforts are underway to devise better opioid delivery systems and dose forms to reduce the ability of abusers to tamper with prescribed medication. Currently available sustained release opioid preparations contain large, even toxic quantities of medication that may be released rapidly when used inappropriately. Sustained release morphine and oxycodone can become immediate release preparations if crushed, chewed, or combined with alcohol, via concomitant ingestion or physically extracted. Snorting or injecting the extracted components can provide a "high" similar to heroin. Transdermal fentanyl patches contain a gel that may be ingested transbuccally or injected, and even discarded used patches still contain a substantial quantity of active ingredient, making safe disposal an important consideration.[10] Several manufacturers are developing new delivery systems, such as including an encapsulated pellet of the opioid antagonist naltrexone, which would be activated by tampering with the tablet and block the effects of the opioid medication, possibly even inducing withdrawal in the opioid tolerant individual. Other formulation modifications include a tablet that turns into a hard solid mass if tampered with. While these modifications will reduce the abuse potential of many sustained release products, they will not totally eliminate the problem. Opportunity and availability remain important contributors to substance abuse.

Finding ways to minimize prescription drug diversion, particularly when prescribing potent and/or large amounts of opioid for cancer pain or other persistent pain conditions, is an essential social and legal responsibility for the prescribing physician, patient, and their caregivers. A variety of strategies have been proposed to detect and reduce diversion. Some measures are controversial, such as routine **urinary drug testing** (**UDT**) of the patient to detect substance abuse and to determine if the patient is indeed taking the prescribed medication rather than selling it. UDT is regarded by many physicians and patients as a sign of mistrust and a violation of their privacy. (see article by Telliogolu) Other measures are practical and simply reflect evidence of a good medical practice. Simple examples of good prescribing practices include the following guidelines. **When starting a patient on a new opioid, begin with a small quantity of medication**. Should the patient experience side effects or not tolerate the prescribed agent, it will save on cost and reduce the amount of unused medication that has the potential to be diverted. It is

Table 1. Estimated Mentions of Selected Opioid Analgesics: 1997 – 2002 , as Reported in DAWN

Year	Meperidine	Morphine	Hydromorphone	Oxycodone	Hydrocodone	Codeine	Methadone
1997	864	1,300	604	5,012	11,570	7,869	3,832
1998	730	1,955	937	5,211	13,611	6,620	4,810
1999	882	2,217	1,313	6,429	15,252	4,974	5,426
2000	1,085	2,483	1,983	10,825	20,098	5,295	7,819
2001	665	3,403	2,003	18,409	21,567	3,720	10,725
2002	722	2,775	2,667	22,397	25,197	4,961	11,709

Values are expressed in number of estimated mentions. ED visits includes dependence, drugs taken for psychic effects or suicide attempts. Source: Office of Applied Studies, SAMHSA, DAWN, 2003.

not infrequent that a patient will not respond well to one or more opioids, and the unused portions cannot be returned to the pharmacy and should not be accepted by the physician, making it difficult to ascertain proper disposal. (Table 2). **Patients should be advised about the potential risks of opioid diversion by family, friends, and other caregivers**. They may contact the Department of Health to insure proper disposal of unused medication, and should be urged not to leave the unused supply sitting on the counter or in their medicine chest. It is advisable to include the direction "lock this medication up" directly on the prescription to document that the instructions were clearly delivered to the patient. Surveys of college students consistently show that 60-70% gain access to prescription opioids from medications prescribed to family members and friends.[12] It may also help to write "Pharmacist to consult on medication safety" on each prescription to reinforce the dangers of mixing medications and the need for security in storing the medication. Risk of serious adverse events increase with the number of different medications taken. While patients are encouraged to use only one pharmacy, they often get certain medications less expensively from different sources, including mail-order suppliers. In addition, patients with chronic pain often have co-morbid problems of depression/anxiety, and sleep disorders. These patients are likely to have more prescription needs and are probably more likely to be doctor and pharmacy shopping. Drug-related fatalities usually involve the ingestion of several prescription CNS depressants, often in addition to alcohol. Every patient must be warned about the serious risks of consuming alcohol with opioid prescription medications.

Physicians prescribing opioids must carefully document the dates and amounts prescribed. Good record-keeping is essential to ascertain that the proper amount of medication is being consumed. This is particularly true for patients obtaining a 3-month supply of a controlled substance from a mail order supplier. Further, strongly advise the patient to have prescriptions filled at only one pharmacy to aide in monitoring the pattern of use. In dealing with high-risk individuals, it helps to establish open lines of communication with the pharmacist to aide in identifying other physicians providing opioid analgesics for these patients. Another simple guideline is to emphasize that only one physician should prescribe opioid medication. Patients seeking opioids from multiple sources should be regarded as high risk for substance abuse. Doctor shopping patients are often difficult to detect, and with HIPPA regulations, it has become increasingly difficult to share healthcare information. Government efforts to monitor controlled substance prescribing have typically been met with skepticism. While central monitoring can improve the detection of medication abusers, it tends to have a negative impact on physician prescribing practices. Rhode Island has an electronic controlled substances monitoring system which captures data on controlled substances prescribed within the state. At present, there is no direct feedback to providers to assist in guiding prescribing practices; however, to monitor high-risk patients, the physician can gain access to patient data by contacting the RI Department of Health. This system will not capture prescriptions filled across state borders or via mail order/internet pharmacies. Thus, vigilance, ongoing assessment, and intelligent prescribing practices are crucial to successful pain treatment and to avoid drug diversion.

Gourlay and associates have proposed "Universal Precautions" for pain medicine prescribing.[13] This approach is based upon 10 principles focusing on careful assessment, continued monitoring, and reevaluation.

1. Make a careful diagnosis of the pain source. Assess co-morbid conditions, such as depression, and include them in the treatment plan. Psychiatric and substance abuse disorders must be addressed.
2. Assess the risk of substance abuse, including family history, current environment, and personal history of substance abuse. Urine drug testing may be considered, with appropriate counseling of the patient regarding illicit drug use. Some experts advocate screening everyone as part of a random process, others restrict it to problematic patients. Not infrequently, some individuals are found not to have detectable levels of the prescribed opioid, suggesting the possibility of diversion. However, no action should be taken on a single aberrant test. Patient counseling and continued monitoring should be performed.
3. Obtain informed consent. Long-term opioid therapy for chronic pain carries the potential for withdrawal, and may be contentious. In addition, the consequences of opioid therapy, including constipation, reduced testosterone levels, fatigue, etc…, should be disclosed. A sample consent/agreement from may be found at: http://www.painmed.org/pdf/opioid_consent_form.pdf

4. A signed treatment agreement is recommended defining the obligations of the physician and patient is helpful in defining the parameters to guide the continuation of opioid therapy and for discontinuation. This avoids arguments and misunderstandings.
5. Document pain levels prior to and after the initiation of opioid therapy. It is essential to document an effective analgesic response to warrant continued treatment. Pain scales are not always the best measure, but other functional improvements may be useful in assessing the treatment response.
6. Initiate an appropriate trial of medication, including opioids and adjuvant analgesics.
7. Frequently reevaluate measures of efficacy. Seeking corroboration from family members and significant others can help to provide a better picture of treatment success, or of failure.
8. Regularly assess the 4 A's of pain treatment: analgesia, activity, adverse effects, and aberrant behavior.
9. Periodically reevaluate the patient's underlying condition and any co-morbid conditions.
10. Documentation! The physician and patient's best protection from legal entanglement is careful documentation of the treatment plan and monitoring efforts.

Opioid analgesics should not be confused with quality pain treatment! Opioid medications remain one of our most effective treatments for pain, but they are not the best and only solution for every patient. Cognitive/behavioral therapy, supervised exercise programs, interventional pain treatments, and nonopioid analgesic medications should be incorporated into an individualized treatment program. When appropriate, an opioid medication trial is a reasonable consideration. When dealing with persistent pain, both the patient and physician should have realistic expectations and goals. Clinical pain trials consistently demonstrate that opioid treatment can improve the patient's pain and global sense of well-being. That being said, few patients will become pain free, and most will continue to report elevated pain scores, despite aggressive opioid administration. Long-term opioid therapy should be guided to reduce suffering, improve quality of life, but not with the expectation of completely eliminating pain sensation. Guiding the patient's expectations in this area is essential.

Table 2. Office of Drug Control Policy: New Guidelines for Prescription Medication Disposal

- Take unused, unneeded, or expired prescription drugs out of their original containers
- Mix the prescription drugs with an undesirable substance, like used coffee grounds or kitty litter, and put them in impermeable, non-descript containers, such as empty cans or sealable bags, further ensuring that the drugs are not diverted or accidentally ingested by children or pets
- Throw these containers in the trash
- Flush prescription drugs down the toilet only if the accompanying patient information specifically instructs it is safe to do so
- Return unused, unneeded, or expired prescription drugs to pharmaceutical take-back locations that allow the public to bring unused drugs to a central location for safe disposal

The FDA advises that the following drugs be flushed down the toilet instead of thrown in the trash:

Actiq (fentanyl citrate)
Daytrana Transdermal Patch (methylphenidate)
Duragesic Transdermal System (fentanyl)
OxyContin Tablets (oxycodone)
Avinza Capsules (morphine sulfate)
Baraclude Tablets (entecavir)
Reyataz Capsules (atazanavir sulfate)
Tequin Tablets (gatifloxacin)
Zerit for Oral Solution (stavudine)
Meperidine HCl Tablets
Percocet (Oxycodone and Acetaminophen)
Xyrem (Sodium Oxybate)
Fentora (fentanyl buccal tablet)

http://www.whitehousedrugpolicy.gov/drugfact/factsht/proper_disposal.html

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Frederick W. Burgess, MD, PhD, is Chief, Anesthesia, Providence VA Medical Center, and Clinical Associate Professor of Surgery (Anesthesia), the Warren Alpert School of Medicine.

Jayne Pawasauskas, Pharm D, BCPS, is Clinical Associate Professor, the University of Rhode Island College of Pharmacy.

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Correspondence

Frederick W. Burgess, MD, PhD
Providence VA Medical Center
830 Chalkstone Ave.
Providence, RI 02908
e-mail: FWBurgessMD@aol.com

Overdose Prevention: Naloxone with Long Acting Opioids

Sarah Bowman, Michelle McKenzie, MPH, and Josiah Rich, MD, MPH

During the past decade the prescription of long-acting opioids to treat a variety of persistent pain conditions in the United States has increased.[1,2] Nationally, the **Centers for Disease Control and Prevention** (**CDC**) tracks a parallel rise in accidental deaths related to prescription opioids during this period.[3] Based on medical examiner data, states participating in the **Drug Abuse Warning Network** (**DAWN**) report that the number of unintentional deaths involving prescription opioid analgesics has surpassed those due to illicit drugs.[4] With increased availability comes the heightened risk that prescription drugs will be accidentally ingested, misused, abused or diverted. Prescribing physicians have the opportunity to respond to this threat with preventive measures including education and prescribing naloxone to any patients who receive long-acting opioids.

Naloxone hydrochloride is an opioid antagonist routinely used by emergency medical personnel to rapidly and safely reverse opioid-induced respiratory depression. It has also been prescribed directly to individuals at risk of an opioid overdose, through naloxone prescription and distribution programs. Participants in naloxone prescription and distribution programs are trained in overdose prevention, identification and response, including calling 911, rescue breathing and naloxone administration. Naloxone is an inexpensive, non-scheduled prescription drug with no agonist properties or potential for abuse.[5-7] Administered to someone using opioids, naloxone may induce acute withdrawal, including symptoms of nausea, vomiting, distress, diarrhea, pain and agitation and less frequently pulmonary edema. Those symptoms are preferable to accidental overdose death. However, when someone is near death due to underlying terminal illness there may be circumstances in which the medication should not be used. For many individuals prescribed long acting opioids and for family members who may accidently or inappropriately access these medications, quick access to naloxone is a safe option, and may be a critical step towards reducing unintentional opioid overdose deaths. Across the country, naloxone has been prescribed and distributed to illicit injection drug users, who have successfully administered to their peers with low rates of reported complications.[8-14] (Table 1) The positive outcomes from community-based naloxone prescription and distribution programs encourage medical professionals to learn from the example of harm reduction programs and to reduce accidental overdose by following naloxone prescription protocols for patients receiving high dose opioids.

Targeted outreach to illicit opioid users for overdose prevention misses a large section of the population who may also be at risk for an accidental opioid overdose. Recipients of prescription opioids are at risk to misuse or abuse these medications, and may benefit from take-home prescription naloxone. Hospitals, medical clinics and physicians' offices provide an ideal contact for many individuals who should have access to this potentially life-saving resource. We recommend that doctors prescribing opioids for pain management consider prescribing naloxone and inform their clients of its proper use in the event of an accidental overdose. As is the case in existing programs, basic information must be conveyed to patients who are receiving prescription naloxone. (Table 2).

Standard practice calls for potential risks or side effects to be explained when a new medication is prescribed. Nonetheless, the patient may not fully understand this information. The process of prescribing naloxone provides a teaching opportunity to emphasize the potential risks of prescription opioids. An additional benefit may be the reduced risk of overdose with the extra information given to patients.

Practical implementation of naloxone prescription would require that individuals receiving the prescription, or their caretakers, be trained in its use and given written instructions that someone else could follow in the event of an emergency. Emergency naloxone prescribed for home use is analogous to the common prescription of epinephrine (Epi Pen) for anaphylaxis, rectal valium (Diastat) for seizures, and glucagon for hypoglycemia. These medications are prescribed to individuals with written instructions that a friend or family member may need to follow.

Project Lazarus[15] in Wilkes County, North Carolina, provides a model for the widespread prescription and distribution of naloxone in physicians' offices, hospitals, pharmacies, detox clinics, prisons and emergency rooms, to patients at risk

Table 1. Large and Established Naloxone Prescription and Distribution Programs in the United States (February 2006)

City/State	Year of establishment	Number of trainings/prescriptions	Number of reported overdose reversals
Chicago	1999	4,600	416
New Mexico	2001	1,312	222
San Francisco	2003	650	141
Baltimore	2004	951	131
New York City	2005	938	73

Sporer KA, Kral, *Annals Emerg Med* 2007; 49: 172-7.

Table 2. Overdose prevention education should include:

1. Signs and symptoms of an opioid overdose.
2. Calling 911
3. Recommendation to consider further training in rescue breathing or CPR
4. Instructions for safe Naloxone administration and storage

Table 3. Potential Indication/Patient Population
(*a partial list, those pertaining to prescription pain management*)

High dose opioid prescription (>100 mg of morphine equivalence/day)

Any methadone prescription to opioid naive patient

Any opioid prescription concurrent with:

- smoking/COPD/emphysema or other respiratory illness or blockage
- renal dysfunction or hepatic disease
- known or suspected concurrent alcohol use
- concurrent benzodiazepine use
- concurrent SSRI or TCA anti-depressant prescription

Table 4. The First Nasal Naloxone Prescription Programs in the United States (July 2007)

City	Year of establishment	Number of trainings/ prescriptions	Number of reported overdose reversals
Boston, MA	2006	283	48
Albuquerque, NM	August, 2007	NA	NA
Cambridge, MA	August, 2007	NA	1

Personal communication with Maya Doe-Simpkins 8/31/2007, Bernard Lieving 8/31/2007, and Louise Rice 9/11/2007.

for opioid poisoning. Throughout Wilkes County, providers will prescribe intranasal naloxone to patients who fit within 14 subpopulations identified as potentially benefiting from prescription naloxone; e.g., patients at risk for taking prescription opioids incorrectly as well as non-medical opioid users. (Table 3)

Non-medical opioid use refers to the recreational use of illicit or prescription opioids including the use of a prescribed opioid by someone other than the patient. Project Lazarus, a component of the region's Chronic Pain Initiative, is the first widespread prescription naloxone program in the United States; this groundbreaking project sets a new standard of care for pain management.

Naloxone is available for both intramuscular and intranasal administration. In both forms it has been successfully administered for peer reversal of an opioid overdose. Intranasal naloxone is used by emergency departments throughout the country, and is distributed through the overdose prevention programs in Massachusetts, New Mexico and now Project Lazarus in North Carolina. Although intranasal naloxone has not been studied as thoroughly as intramuscular, life-saving results point to its success. (Chart 4). Researchers have found limited data supporting the use of intranasal naloxone prescribed for patient use,[16] yet field experience in Massachusetts and New Mexico indicates that this option provides a viable alternative for practitioners who are hesitant to distribute or prescribe needles for their patients.

Extensive experience with the prescription and distribution of naloxone to patients receiving high dose opioids is not available; nonetheless, data from overdose prevention programs targeting injection drug users document the life-saving potential of naloxone administered by friends and family. Further evaluation of naloxone to prevent overdose in patients receiving long acting opioids needs to be done. Findings from Project Lazarus will contribute to this process. Expansion of pain management guidelines to establish specifications for education about overdose prevention including the prescription of naloxone will increase access to changing standards of care. At this time, there is sufficient evidence to promote patient education around overdose prevention including the use of prescription naloxone, as well as including naloxone prescription into pain management guidelines.

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Sarah Bowman is a research assistant, The Miriam Hospital.

Michelle McKenzie, MPH, is Senior Project Director/Research Associate, The Miriam Hospital/Warren Alpert Medical School of Brown University.

Josiah Rich, MD, MPH, is Professor of Medicine and Community Health, The Miriam Hospital/Warren Alpert Medical School of Brown University.

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Discussion of off-label usage

Intranasal naloxone administration

Correspondence

Michelle McKenzie, MPH
Miriam Hospital,
164 Summit Ave
Providence, RI 02906
e-mail: MMcKenzie@lifespan.org

Methadone Analgesia for Persistent Pain: Safety and Toxicity Considerations

Frederick W. Burgess, MD, PhD, and Jayne Pawasauskas, Pharm D, BCPS

Methadone, a synthetic mu-opioid agonist with a uniquely prolonged and variable elimination half-life, was developed in Germany during the Second World War. However, not until Dole and Nyswander introduced the concept of using methadone as a treatment for heroin addiction in 1965 did methadone gain a role in clinical practice.[1] Due in part to its association with drug addiction, methadone found little application as an analgesic in routine medical practice. Even today, many patients, fearing the label of " drug addict", are reluctant to accept a prescription for methadone. Furthermore, many physicians mistakenly believe that they cannot prescribe methadone for pain without a special DEA license to treat addiction. Despite these barriers, methadone prescribing for chronic and cancer pain has been showing a gradual increase.[2,3] Efforts to promote greater use of opioid analgesics for cancer pain treatment spawned the development of sustained release morphine and oxycodone. The ability to deliver continuous opioid blood levels greatly improved the comfort and quality of life for many cancer patients. Unfortunately, the expense of the sustained release patented opioid preparations limited accessibility, resulting in renewed interest in methadone as a cheap generic alternative opioid capable of providing sustained blood levels with convenient dosing intervals.

In excess of 200,000 individuals are managed at methadone treatment programs throughout the US.[4] Until recently, opioid treatment programs accounted for the vast majority of methadone consumption in the US. Methadone prescribing for pain conditions, while lagging initially, has shown a consistent increase in prescriptions throughout the 1990s.[5] **The Food and Drugs Administration's (FDA) ARCOS** (Automation of Reports and Consolidated Orders System) data on methadone delivery in the US amounted to 518,737 grams in 1997, increasing to 6,621,687 grams in 2006. Mirroring the rise in methadone consumption, was an equally dramatic increase in unintentional deaths linked to methadone. Unintentional prescription overdose deaths occur predominantly with hydrocodone, oxycodone, and methadone. CDC data for 1979-1990 revealed an average increase in the death rate of 5.3%; however, from 1990-2002 the unintentional drug overdose rate increased by 18% per year.[6] During that latter period, prescription opioid deaths increased by 91%, with heroin related deaths increasing by only 12% for the same period. In 2002, prescription opioids contributed to 4,451 deaths, as opposed to 1061 deaths linked to heroin. These statistics reveal the alarming increase in the misuse and abuse of prescription opioids, which are second only to marijuana as substances of abuse. As indicated above, hydrocodone, oxycodone, and methadone are the three most common agents implicated in overdose deaths.[7] Methadone has been involved in approximately one-third of all prescription drug overdose deaths, despite the fact that it is prescribed far less than oxycodone.

In considering the long half-life of methadone in the body, it is important to recognize that dosage adjustments must be made slowly.

Several factors may account for the apparent increased hazard. First, methadone is extensively employed in the treatment of chronic substance abusers. The presence of methadone may reflect concurrent polysubstance abuse in clients undergoing methadone maintenance therapy. Second, methadone has a prolonged elimination profile, which may prove uniquely hazardous when taken concurrently with alcohol and other central nervous system depressants. Although methadone doses of 80-120mg/day are common in the management of opioid addicts, the naïve abuser may potentially develop respiratory depression after a single 50mg dose. Third, methadone is able to prolong the rate-corrected **QT interval (QTc) of the cardiac cycle**, potentially triggering a lethal *torsades de pointes* arrhythmia, a form of polymorphic ventricular tachycardia. Prolongation of the QTc appears to be dose-related, most evident when the methadone dose exceeds 120mg daily. However, the potential for lethal drug combinations, such concomitant therapy with various antipsychotics, antibiotics, antidepressants, antifungal agents, and a wide variety of other pharmacologic agents may additively prolong the QTc or inhibit the metabolism of methadone resulting in marked elevation of the blood level. Coexisting factors, such as familial prolonged QTc syndromes, hypokalemia, hypomagnesemia, female gender, and preexisting cardiac disease, are likely to increase the risk of lethal arrhythmias.

Methadone Pharmacology

Methadone is a lipid soluble, basic compound that exhibits excellent bioavailability. Absorption after oral tablet ingestion results in peak blood levels at around 3 hours, with approximately 85% absorption. Methadone is a chiral compound, with only the racemic mixture available in the US. R-methadone isomer is a potent mu and delta opioid agonist, and is available in Germany as a distinct product. S-methadone has no mu-opioid activity; however, it does exhibit some potentially useful properties for the treatment of pain and addiction. S-methadone is an antagonist of the **N-methyl-D-aspartate (NMDA)** glutamate receptor, which may play an important role in reducing opioid tolerance, and in providing analgesia much like ketamine. S-methadone also appears to block the reuptake of serotonin and norepineph-

Table 1. Methadone Drug Interactions Contributing to Cardiac Toxicity [a]

Class	Interaction
ANTIBIOTICS	
Fluoroquinolones (ciprofloxacin, moxifloxacin)	Increase methadone levels through CYP 450 enzyme inhibition (3A4); also have causal relation to QT prolongation
Macrolides (erythromycin, clarithromycin)	
Rifamycins (rifampin, rifapentine)	Decrease methadone levels through CYP 450 enzyme induction
ANTIFUNGALS	
Ketoconazole, itraconazole, voriconazole, fluconazole	Increase methadone levels through CYP 450 enzyme inhibition (2C9, 2C19, 3A4)
ANTIDEPRESSANTS	
Tricyclic antidepressants (amitriptyline, desipramine)	May contribute directly to QT prolongation
Selective serotonin reuptake inhibitors (fluvoxamine, sertraline, fluoxetine)	Increase methadone levels through CYP 450 enzyme inhibition (3A4, 2C, 2D6 to varying degrees)
ANTICONVULSANTS	
Carbamazepine, phenytoin	Decrease methadone levels through CYP 450 enzyme induction (3A4)
ANTIOVIRALS	
Efavirenz, nelfinavir, amprenavir, darunavir	Decrease methadone levels through CYP 450 enzyme induction (3A4)
Ritonavir	May increase methadone levels initially; decrease methadone levels with prolonged use through CYP enzyme induction (3A4)
ANTIPSYCHOTICS	
Phenothiazines, haloperidol, droperidol, risperidone, ziprasidone, quetipaine	Additive inhibition of repolarization resulting in QT prolongation

[a] Not a complete list of all potential methadone/drug interactions. Adapted from: *Clinical Pharmacology Online*. Methadone monograph – interactions. Retrieved February 21, 2008. Available at www.clinicalpharmacology.com and Hansten PD, Horn JR. The Top 100 Drug Interactions – A Guide to Patient Management. 2007 Edition. Freeland, WA: H&H Publications; 2007.

rine, which may contribute to analgesia as well. For these reasons, methadone is often recommended for the management of neuropathic pain.

Methadone exhibits a fairly large volume of distribution, with a prolonged elimination phase. The elimination profile reveals an initial alpha phase of 8-12 hours, followed by a very prolonged beta elimination phase of 30-60 hours. This pattern accounts for the more frequent every 8-hour dosing pattern required for pain treatment vs. the once-daily dosing employed in the treatment of addiction. The prolonged lower blood levels obtained with once-daily dosing are sufficient to block opioid withdrawal, but are inadequate for analgesia. Elimination of methadone occurs predominantly via hepatic biotransformation. The **cytochrome P450** (**CYP**) isozymes, predominantly CYP3A4, demethylate the parent compound. Other enzymes, including CYP2B6 and CYP2D6 participate to a lesser extent.[8] Methadone accumulation does not appear to be problematic in the setting of renal failure or stable hepatic disease. Methadone appears to develop large tissue reservoirs, which may confound the interpretation of blood levels in overdose cases, due to re-equilibration into the bloodstream.[9]

In considering the long half-life of methadone in the body, it is important to recognize that dosage adjustments must be made slowly. Steady state blood levels are generally not achieved until after 4-5 half-life intervals. Because methadone may take up to a week to equilibrate, rapid escalation of the dose can lead to the development of toxicity 3 days after the last adjustment. Patients accustomed to the rapid titration of most short-duration opioids can be at risk if they are not carefully educated to avoid self-titration and to adhere rigidly to the prescribed dose.

Toxicity

As with any opioid, methadone shares a similar pattern of toxicity and side effects, most of which are directly attributable to activation of an opioid receptor. Common toxic manifestations include: constipation, nausea, vomiting, sedation, pruritis, bradycardia, and respiratory depression. Respiratory depression is believed to contribute to most opioid-related deaths. Respiratory depression is dose related, but varies greatly between individuals, influenced by prior opioid exposure, concomitant use of central nervous system depressants, the intake of drugs that may alter the metabolism of methadone, and co-existing conditions, such as sleep apnea. Some degree of tolerance appears to develop to the respiratory depressant effects of opioids; however, this is incomplete, and evidence suggests that worsening of sleep apnea occurs in a dose-dependent fashion.[10] The one unique aspect to metha-

done is the prolonged rise in the blood level, which may result in a more insidious onset of the respiratory depression.

Mounting evidence has shown a relationship between methadone and prolongation of the QTc interval.[11,12] Studies in asymptomatic patients receiving methadone reveal a tendency toward prolonged QTc intervals, especially with doses exceeding 120mg.[13] However, torsades has occurred in individuals over a wide range of doses, in some cases as low as 60mg, based on data reported to the FDA.[12] Intravenous administration of methadone may be associated with a greater risk of QTc prolongation, possibly due to the preservative chlorobutanol, which also inhibits the hERG potassium channel.[14] Based on this information, screening electrocardiograms should be considered in most individuals receiving methadone in dosages greater than 120mg. Serial electrocardiograms should be considered as the dose level is escalated to assess the QTc interval, particularly when other pharmacologic agents known to impact the QTc interval are prescribed. (Table 1)

Prescribing Methadone

Methadone appears to be a useful alternative in the management of refractory cancer pain.[3,15,16] There is also considerable support, at least from a mechanistic point of view, for its use in the management of neuropathic pain refractory to other interventions.[2] Initiating methadone for pain treatment in the opioid-naïve patient should begin with a small dose of 2.5-5mg at 8-12 hour intervals. The guiding principle should be "*start low and go slow*". Small adjustments of 2.5 mg per day are reasonable in this setting. Remember that methadone peak plasma levels will not achieve steady state for 3 to 5 days in most individuals. Furthermore, as methadone tissue stores build, the half life will tend to increase.

Most opioids display incomplete cross-tolerance. When converting between oxycodone and morphine, the calculated 24-hour equivalent dose should be reduced by 20-30%. However, with methadone, the calculated 24-hour dose may need to be reduced as much as 90% or more. The higher the preexisting dosage of opioid, the greater the reduction in the recommended starting methadone dose. Two methods of rotation may be employed when rotating to a new opioid. The first involves "stop and go", by halting the delivery of the previous opioid and initiating a calculated equivalent 24-hour dose in divided intervals, with a supplemental dose for inadequate analgesia. The second approach is to gradually taper the existing opioid by one-third daily, and gradually escalate a conservative dose of methadone 2.5-5mg every 8 hours. This approach is probably more convenient when dealing with patients receiving intravenous opioids than oral sustained release dose forms. Several protocols for switching to methadone have been published.[17-21] The dose of the 24 –hour equivalent of the starting opioid helps determine which protocol to use. For example, one source used linear regression to analyze 5 protocols and develop a formula, referred to as the "rule of 15."[22] This formula (estimated oral methadone dose per day (mg) = oral morphine equivalent dose per day (mg) ÷ 15 + 15) can be used for a patient taking daily equivalents of 60 – 1200 mg of oral morphine. Another formula should be used for patients falling outside these parameters. These formulas are not exact. Rather, they provide a safe starting point, or dose estimation, from which to adjust treatment. Patients need to be educated regarding the toxic nature of methadone, stressing the importance of keeping their medication in a locked secure location. Individuals receiving doses of 120mg or greater should be monitored with serial electrocardiograms prior to dose adjustments. Patients receiving high doses, greater than 300mg/day, are at risk for cardiac events, and further escalation in the dose may be inadvisable without careful evaluation.

Conclusion

Methadone is an effective analgesic with unique properties that set it apart from most other opioids. These unique aspects, the prolonged duration of action, NMDA receptor inhibition, and catecholamine reuptake inhibition appear to provide improved analgesia, but also carry the risk of a unique toxicity profile. When applied cautiously, methadone has great value as an analgesic for cancer and other persistent painful conditions

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Frederick W. Burgess, MD, PhD, is Chief, Anesthesia, Providence VA Medical Center, and Clinical Associate Professor of Surgery (Anesthesiology), The Warren Alpert Medical School.

Jayne Pawasauskas, Pharm D, BCPS, is Clinical Associate Professor, University of Rhode Island College of Pharmacy.

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Correspondence

Frederick W. Burgess, MD, PhD
Providence VA Medical Center
830 Chalkstone Ave.
Providence, RI 02908
e-mail: FWBurgessMD@aol.com

Postoperative Pain Management for the Opioid-Tolerant Patient

Frederick W. Burgess, MD, PhD, and Andrew Maslow, MD

As we approach the end of the Decade of Pain Control and Research, healthcare monitoring organizations, such as the Joint Commission for the Accreditation of Healthcare Organizations, have promulgated standards for the evaluation and treatment of pain, thereby improving the documentation, assessment and treatment of pain. The medical profession has in turn provided greater access to analgesic medications, especially the opioid class. Opioid prescribing and consumption have soared, particularly in the realm of cancer pain and other persistent pain conditions.[1] As a result, many preoperative surgical patients present with a history of long-term opioid consumption and preexisting tolerance.

The success of chronic opioid administration for cancer pain suggested that analgesia could be maintained over sustained periods in the majority of patients. However, mounting evidence suggests that long-term opioid use reduces opioid analgesic efficacy pain and may lead to increased pain sensitivity. Doverty and associates, using the cold pressor test pain model, documented a reduced pain threshold and hyperalgesia in methadone maintenance patients.[2] This population displays considerable cross-tolerance to morphine. Although they will receive larger doses of opioid than the opioid naïve population, their pain control is significantly poorer.[3] Rapp and colleagues compared the pain response and analgesic consumption of a series of subjects treated with long-term opioids undergoing surgery to a matched control population.[4] Employing a liberal intravenous patient-controlled analgesia regimen for postoperative pain, they found that patients taking long-term opioids consumed, on average, 3 times more opioid. Despite this large opioid intake, pain control in the chronic opioid group was significantly worse than the matched controls. The authors concluded that pain scores in the chronic opioid group do not entirely reflecte the patient's comfort level. DeLeon-Casasola and colleagues noted a similar pattern in postoperative surgical patients using chronic opioids, who were treated with epidural opioid infusions.[5] They also found that chronic opioid users required 3 times the usual epidural opioid dose for adequate analgesia.

Pain scales tend to be consistently inflated in the persistent pain population.[4] More global measures of patient distress may be more useful in guiding treatment than targeting specific pain score targets.[6] Assessments of a patients' ability to participate in their rehabilitation program, to obtain restful sleep and, their amount of suffering are useful to help guide opioid administration. Most patients will respond honestly if asked whether their pain level is tolerable. Unfortunately, unrealistic expectations of complete pain relief increase the risk of respiratory depression and other opioid-induced side effects. While tolerance to the analgesic effects of opioid medications can develop rapidly, tolerance to opioid side effects such as respiratory depression, and constipation is less complete.[7]

Substantial evidence suggests hat good perioperative pain control improves outcome, hastens return to baseline function, and reduces healthcare costs. For some chronic opioid users, their pain may be directly related to their pending surgical intervention, such as painful osteoarthritis leading to joint replacement, or lumbar spine surgery. In most of these patients, the surgical intervention will ultimately improve their pain, but in the short-term, they present considerable challenge to the anesthesiologist and surgeon. The burden falls on caregivers to satisfy their comfort needs and elevate their function in the immediate postoperative period. The following discussion will review pain management options in the perioperative period, with emphasis on chronic opioid users.

Anesthetic Options to Reduce Postoperative Pain

Anesthetics, aside from the opioids, provide direct analgesic effects through non-opioid pathways, or indirectly modulate the opioid receptors to reduce tolerance and improve opioid efficacy. Examples include nitrous oxide and ketamine.[8,9] Both are antagonists of the glutamate **N-methyl-D-aspartate (NMDA)** receptor, which modulates sensory neuronal activity in the spinal cord. The NMDA receptor appears to play an important role in the amplification of the sensory pain signal through a mechanism referred to as "wind-up". In addition, the NMDA receptor is involved in the development of opioid tolerance. Thus patients treated with nitrous oxide or ketamine as part of their anesthetic regimen experience less postoperative pain and require less opioid analgesic.[10]

In the early 1990s, "preemptive analgesia" (the early administration of analgesics prior to the onset of pain) was thought to disrupt the "wind-up" phenomena at the spinal cord level and reduce postoperative pain.[11] Local anesthetics are the only pharmacologic agent capable of completely blocking pain sensations, at least temporarily, and have been found to be useful in reducing opioid requirements in some circumstances. Local anesthetics may be administered via wound infiltration, nerve blockade, or central neuraxis blocks (spinal or epidural). Regional anesthetic techniques may be used in the operating room, and may be extended into the postoperative period employing in-dwelling catheters for considerable advantage. Although preemptive analgesia using local anesthetics has been reported, this benefit has not been consistently demonstrated.

No preemptive pain benefit has been demonstrated with early (preincision) administration of opioids. While animal models suggested that the administration of opioids prior to surgical trauma could reduce the intensity of pain during the postoperative phase, it has been difficult to replicate opioid preemptive analgesia in humans.[11] In contrast, some studies have demonstrated the development of increased postoperative pain and analgesic requirements in patients treated with high-dose opioid infusions during surgery.[12] High-dose remifentanil and fentanyl infusions appear to contribute to

increased postoperative pain and opioid consumption, suggesting rapid onset of opioid tolerance during the early postoperative period.[12,13] The development of rapid opioid tolerance is not inconsistent with other animal models and clinical studies which confirm the rapid onset of tolerance, as well as the development of hyperalgesia with prolonged or high-dose opioid exposure.[14-16] Thus, a balanced analgesic technique utilizing nonopioid analgesic regimens, alone or in combination with low-dose opioids, may aide in preserving opioid efficacy, reducing opioid consumption, and improving postoperative pain control.

Alternative Analgesic Strategies

Strategies to reduce postoperative pain and escalating opioid use in chronic opioid users need to consider individual patient and surgical factors. In most settings, it is probably unwise to have the patient stop his analgesic medications prior to surgery. Poorly controlled preoperative pain is associated with difficult pain management in the postoperative phase. This can be prevented by continuing the regular pain medication already prescribed. The practice of stopping all NSAIDS two weeks prior to surgery is to be condemned. Long half-life NSAIDS may be discontinued in favor of shorter acting agents, such as ibuprofen. Ibuprofen need only be discontinued 24-48 hours prior to surgery if bleeding is a concern. An alternative approach is to consider the use of celecoxib, the only cyclooxygenase-2 inhibitor still on the market, as it does not interfere with platelet function. A single preoperative dose on the morning of surgery and subsequent doses during the postoperative can improve pain symptoms and potentially diminish opioid requirements.[17,18]

As noted, some anesthetic agents can improve pain and reduce opioid demand, if incorporated into the patient's anesthetic plan. A meta-analysis supports the use of ketamine, 0.5mg/kg during anesthetic induction or shortly before incision to reduce opioid consumption and side effects during the early postoperative phase.[19] This may be uniquely helpful in patients who were employing chronic opioids prior to surgery, to reduce opioid tolerance. In addition, nitrous oxide may be included as a component of the anesthetic, because its action as an NMDA antagonist appears to contribute to improved postoperative pain with few major side effects.[9]

The practice of stopping all NSAIDS two weeks prior to surgery is to be condemned.

Regional anesthetic techniques reduce postoperative pain and opioid consumption. The use of regional nerve blocks, such as femoral, sciatic, and various brachial plexus nerve blocks for extremity procedures can offer an extended period of analgesia following surgery. Epidural local anesthetic/opioid infusions provide very effective analgesia following thoracic or upper abdominal surgery.[20] Benefits include improved pulmonary function, a stronger cough, and, in some studies, a reduced need for postoperative mechanical ventilation. Although most complicated pain management patients will require supplemental opioids, their pain control will be substantially improved by employing spinal or epidural analgesics. Furthermore, attempts to eliminate opioid analgesics in the chronic user prior to surgery is not desirable, and increases the risk of developing opioid withdrawal symptoms, despite obtaining good pain relief from central neuraxial opioids. **As a general rule, chronic opioid users should be maintained on their preoperative dose of opioids during the postoperative phase, at a minimum! If no other analgesic method is employed, it is reasonable to anticipate that these patients will require supplemental opioids exceeding 2-3 times their usual intake**.

While the analgesic value of local anesthetics is well recognized when applied directly for neural blockade, local anesthetics may also be of considerable value as an intravenous analgesic. Intravenous lidocaine has been employed in a variety of chronic pain conditions. Recent evidence shows that intravenous lidocaine is useful as a postoperative analgesic. Patients undergoing intestinal surgery treated with a continuous postoperative lidocaine infusion (2mg/min) experienced less pain and obtained a more rapid recovery of bowel motility following surgery.[21] Lidocaine infusions for postoperative pain are often limited to patients in monitored settings due to preexisting nursing protocols originally designed for cardiac arrhythmia management. However, as more experience in this area develops, systemic lidocaine administration may find an important role as a valuable postoperative analgesic adjunct.

Alpha-2 adrenoceptor agonists, such as clonidine and dexmedetomidine can improve pain management significantly.[22] Clonidine has been employed as an epidural analgesic for the treatment of intractable cancer pain and other chronic pain conditions. Recently, dexmedetomidine, an a-2 adrenoceptor agonist which is nearly 8 times more selective for the a-2 receptor than clonidine, is available for intravenous infusion for use as a sedative/analgesic.[22] Initially exploited as a sedative in the critical care setting, dexmedetomidine offers a number of clinical advantages over other sedative agents in the perioperative period.[25] Stimulation of pre-junctional a2 adrenergic receptors inhibits norepinephrine release, and also contributes to increased secretion of GABA from the Locus Ceruleus in the brainstem, resulting in reduced anxiety, sedation and a 'natural' sleep state.[24] Stimulation of a2 receptors of the intermediolateral cell column and substantia gelatinosa of the spinal cord inhibits the release of Substance P resulting in analgesia. When used alone, it does not result in respiratory depression. In addition, it is capable of producing analgesia, a reduction in blood pressure, and a relative bradycardia, all attractive features in the perioperative patient. Dexmedetomidine analgesia is not as profound as the opioids, but does reduce the consumption of opioids and other analgesics. Dosing varies with the clinical scenario. Intravenous doses of 0.2-0.5 mcg/kg may be administered as analgesic supplements, alone or in conjunction with a continuous infusion of 0.2-1.0 mcg/kg/hr. Too rapid administration of larger doses of dexmedetomidine may produce transient elevations in blood pressure, usually followed by a decline. Doses exceeding 1mcg/kg/hr do not cause a decline in blood pressure, and may even cause a small

rise in pressure. Dexmedetomidine will not entirely replace the need for opioids, but may be helpful as an opioid adjunct, reducing side effects and improving analgesia during the perioperative period.

Another atypical analgesic class, are the gabapentinoids. Although introduced as an anticonvulsant, gabapentin, and the newly available analog pregabalin, have found considerable use as analgesics for various neuropathic pain conditions.[26] Gabapentin has recently been exploited as a supplemental analgesic for perioperative pain.[27] A preoperative dose of gabapentin (900-1200 mg) followed by additional doses during the postoperative period allow a reduction in opioid consumption. However, in some trials, gabapentin appeared to contribute to increased postoperative sedation and dizziness. There was evidence of a reduction in opioid related side effects and in overall opioid consumption during the first 24 hours. Gabapentin may be considered as an adjunct analgesic, but the evidence is inadequate to recommend widespread adoption. Further study will be needed to determine which surgical procedures will benefit from this medication, and the optimal dose and duration of treatment.

Conclusion

Patients consuming high-dose opioids on a chronic basis present considerable challenge during the perioperative period. While the opioid class remains our most effective means to provide pain relief, alternative analgesic approaches can be extremely helpful in improving pain control instead of, or in balance with opioids. By controlling factors that influence postoperative pain, such as proper preoperative preparation of patient expectations, continuing the use of preoperative analgesics, appropriate selection of the surgical procedure, and utilization of alternate pain relieving strategies, pain control and patient satisfaction can be achieved in the most challenging patient. As in other areas of medicine, combination therapy can often provide the best effect with the fewest adverse reactions.

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Frederick W. Burgess, MD, PhD, is Chief, Anesthesia, Providence VA Medical Center, and Clinical Associate Professor of Surgery (Anesthesiology), the Warren Alpert Medical School of Brown University.

Andrew Maslow, MD, is Clinical Associate Professor of Surgery (Anesthesiology), the Warren Alpert Medical School of Brown University.

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Discussion of off-label usage

Dexmedetomidine in doses greater than FDA-approved doses

Correspondence

Frederick W. Burgess, MD, PhD
Providence VA Medical Center
830 Chalkstone Ave.
Providence, RI 02908
e-mail: FWBurgessMD@aol.com

The Use of Urine Drug Testing To Monitor Patients Receiving Chronic Opioid Therapy for Persistent Pain Conditions

Tahir Tellioglu, MD

An estimated 5% to 33% patients in primary care settings have chronic non-cancer pain. [1] As many as 90% of patients in pain management settings receive opioid medications.[2, 3] Opioids are powerful and effective analgesics which are important in the management of moderate-to-severe chronic pain that is not controlled with non-pharmacologic therapies and non-opioid analgesics. Primary care practitioners, who do much of the long-term opioid prescribing, are often uncomfortable prescribing opioids to patients with chronic pain, because of the perceived risks of opioid dependency, addiction, abuse and the potential legal consequences.[4] Also, opioids may interact with other prescribed medications or illicit chemicals (i.e. benzodiazepines, alcohol), which may result in life-threatening conditions. Further, patients afflicted with persistent pain tend to underestimate their medication use and provide incorrect information about their illicit drug usage. In a recent retrospective analysis of data from 470 patients who had urine screening at a pain management program in an urban teaching hospital, 45 % of the patients had abnormal urine screens (either for the absence of the prescribed opioid or having an illicit substance in their urine). [5] Therefore, random or regular drug testing is an essential component of pain management with opioid medications as recommended in the model guideline for the Use of Controlled Substances in Pain Management issued by the Federation of State Medical Boards. [6]

Urine Drug Testing

A **urine drug test** (UDT) is a technical examination of urine samples to determine the presence or absence of specified drugs or their metabolized traces. Urine has a 1- to 3-day window of detection for most drugs. Recent use of prescription medications (e.g., opioids, benzodiazepines, amphetamines, barbiturates) and illegal substances (e.g., heroin, cocaine, marijuana, phencyclidine) can be detected in patients' urine.[7,8] It also is low cost and non-invasive, compared to blood testing. Depending on the need, the clinician requests testing whether the presence of any particular substance or group of substances is suspected or expected. One of the commonly used UDT panels is called "Federal Five" drugs or drug classes (marijuana, cocaine, opiates, PCP, and amphetamines), tested in federal employees.[9] Other drugs can be added to the list, depending on the need and the availability of the laboratory technique (methadone, propoxyphene, benzodiazepines, oxycodone, and barbiturates).

Benefits and Limitations of Urine Drug Tests

For most clinical applications, initial UDT is usually done with class-specific immunoassay drug panels. The immunoassay technique, either laboratory based or at the clinic (e.g., "dip-stick" testing), is a rapid testfor drugs in the urine, at lower cost. (Figures 1 and 2) It detects only the classes of drugs such as barbiturates, or opioids, but typically does not identify individual drugs within a class. Further, its ability will vary according to the drug concentration in the urine and the assay's cutoff concentration. Immunoassay is highly predictive of cocaine and its primary metabolite, benzoylecgonine.

Because of the cross-reactivity problems, immunoassay is less reliable for amphetamine/methamphetamine. Immunoassay is very responsive for morphine and codeine, but again, is unable to distinguish which is present. They also usually give false negative results for semi-synthetic/synthetic opioids such as oxycodone, oxymorphone, buprenorphine, fentanyl, and methadone. Specific immunoassay tests for some semisynthetic/synthetic opioids will eventually become available.

Single-use immunoassay devices are available for urine testing of common classes of misused drugs. [10] They are practical, easy to use, offer rapid results, require little training and are inexpensive. However, they often are inadequate in opioid management since they only identify the drug class, not the presence of a specific drug. Further, the devices may lack adequate quality assurance and quality control (e.g., the integrity of the test reagents following transportation and storage).

Laboratory-based UDTs are used to separate the different components and specifically identify the components in a specimen. These techniques, including **gas chromatography/ mass spectrometry** (GC/MS) and **high-performance liquid**

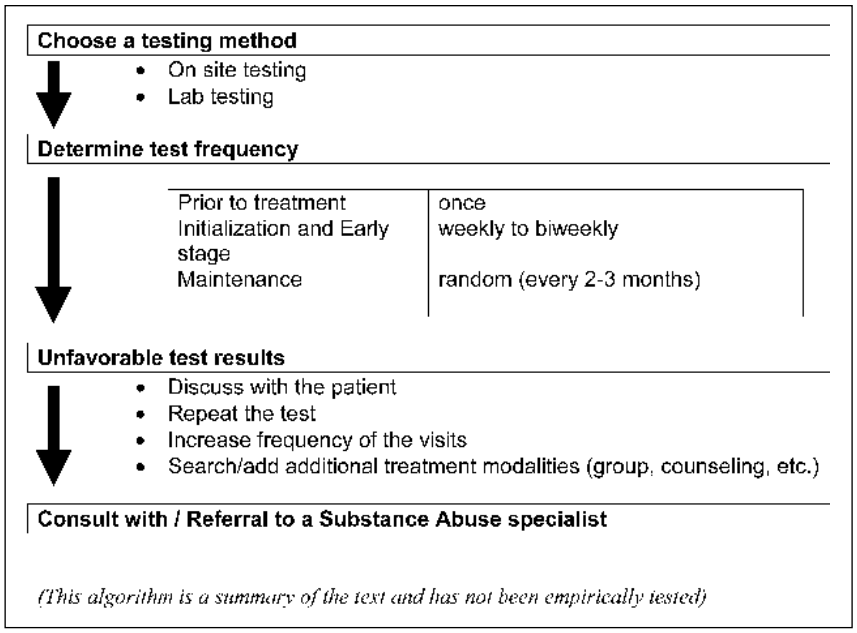

Figure 1. Urine Drug Testing Algorithm for patients on opioid pain medications.

Table 1. Advantages and disadvantages of types of urine drug testing methodology for patients on opioid pain medications

Type:	Advantages	Disadvantages
Immunoassays	• Provide rapid results • small quantities of substances can be detected • permit onsite analysis of test specimens	• lacks specificity to determine which drug in a class is present • problems persist about the chain of custody, provision, stability, and storage of samples • have limitations such as increased cost or reduced accuracy. • Some State regulations disallow onsite test analysis.
Chromatography	• Can determine which drug in a class is present in the sample	• requires relatively large amounts of drugs in specimens require laboratory setting and special facilities

chromatography (HPLC), can confirm a specific drug. Laboratory-based UDTs can also identify drugs that are not detected by immunoassay methods (such as the semi-synthetic opioids hydromorphone, hydrocodone, oxycodone and oxymorphone).

The cost is a concern in urine testing. Unselective UDT (immunoassay technique) is usually much cheaper than the laboratory-based UDT. Among these, dip-stick testing is a rapid test for drugs in the urine, and it has lower cost ($5-10 per test). (Picture 1) On the contrary, the average costs for the laboratory-based UDT are between $100 to $ 200 per test for self-paying patients in Rhode Island. (Reimbursement rates for the insured vary depending on the insurance). Because a test is relatively expensive does not necessarily mean that it is not cost-effective. Cost-effectiveness depends on the speed of obtaining results, the interpretation and clinical use made of them, and, above all, their analytical reliability. While commercial strips eliminate the need for test tubes and incorporate standardized reagents, the instructions and warnings about storage and use are often ignored, and multi- reagent strips are especially liable to be used incorrectly.

Urine Testing for Alcohol Abuse

Alcohol combined with an opioid such as methadone increases the risk of excessive sedation. It is important for practitioners to test routinely for alcohol, to encourage and educate patients of its consequences, and avoid providing opioid medication to patients who abuse it. Alcohol has a short duration in the body and is detectable for less than 12 hours.

While most alcohol is metabolized by alcohol dehydrogenase to carbon dioxide and water, a small portion is conjugated to **ethyl glucuronide (EtG).** EtG can persist in the urine for several days (up to 80 hours). It has been reported as a sensitive and specific marker to detect alcohol use [11], and the test has recently become commercially available. However, alcohol is present in many non-beverage products that can produce a positive result. The use of an EtG test in determining abstinence lacks sufficient specificity for use as primary evidence.

Frequency of Testing

It is generally accepted that each patient should have drug testing during assessment for chronic opioid treatment. The frequency of UDT is based on the patient's condition: testing should provide enough warning time to respond to a potential abuse or misuse. Some drugs such as cocaine can be detected in the urine for 3 days after the last dose, therefore patients may need frequent testing (twice-a-week) to detect such usage. The presence of medications which can interact with the opioids -such as benzodiazepines- should be detected early and their risks and benefits analyzed and documented. Regular testing should be performed more frequently early in treatment, and then continued randomly when patients are stabilized.

Urine collection

In general, 30 ml urine sample is adequate to complete the testing and satisfy requirements. The temperature of a urine sample within 4 minutes of voiding should fall within the range of 90°F to 100°F. Urinary pH should remain within the range of 4.5 to 8.0. Concentrated urine samples are more reliable than dilute samples. Therefore, urinary creatinine less than 20 mg/dL is considered dilute; less than 5 mg/dL is not consistent with human urine. Some patients may falsify test results for secondary gain. Urine samples outside of these ranges should be discussed with the patient and/or the laboratory, as necessary by sound treatment ethics and the overall goals of the program. Direct obser-

Table 2. Checkpoints

- Patients maintained on opioid pain medications should be tested regularly for alcohol and common illicit substances including marijuana, opioids, benzodiazepines, amphetamine, and cocaine.
- Urine drug testing remains the most common method of drug testing; however other drug testing methods are developed.
- Training and educating should be provided to staff members about the benefits and limitations of drug tests.
- Unfavorable drug test results should not be used punitively but should be seen as an opportunity to discuss and modify the treatment approaches accordingly.

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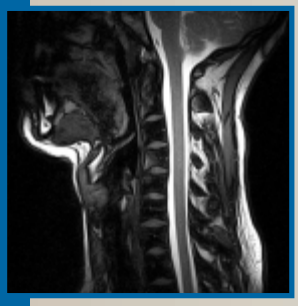

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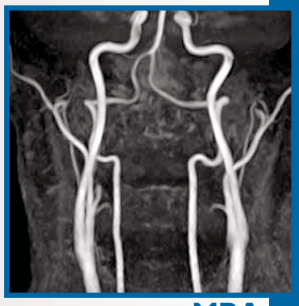

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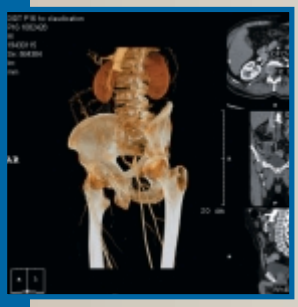

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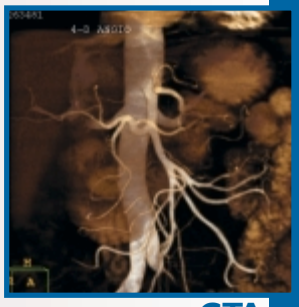

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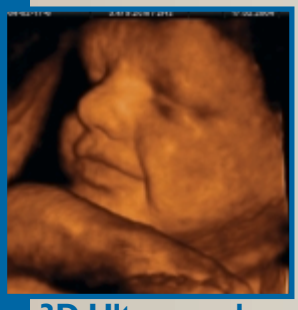

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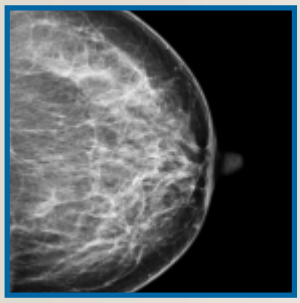

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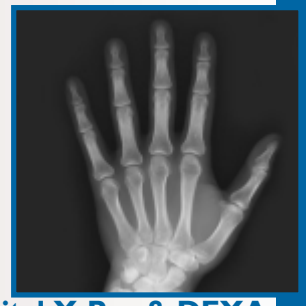

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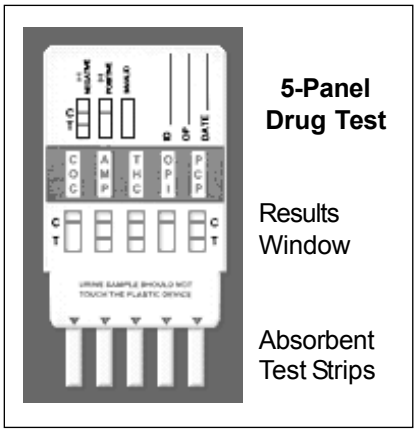

Figure 2: The **5-Panel Drug Screen Test Card**, detects 5 different drug categories, displaying **5 separate results.** The absorbent **Test Strips** are dipped in urine and removed. After 5 minutes, results are displayed in each of 5 **Results Windows.**
2 Red Lines = Negative.
1 Red Line = Preliminary Positive.

vation of urine collection, temperature strips, adulterant checks, and other methods should be used when possible to ensure test validity. All urine samples are commonly checked for pH and temperature. In case there are further concerns regarding the sample validity, the ordering physician may request additional analyses such as urinary creatinine and adulterant checks.

Interpreting and Using Drug Test Results

UDT is a useful clinical tool to document compliance, stability and progress of the treatment. Test results can even help patients to improve social and legal problems. Abnormal results help identify addiction or drug misuse. Test results should be documented in patient records along with appropriate justifications for subsequent treatment decisions. In the event that the UDT results are abnormal or inconsistent, patients should be informed immediately and should be given an opportunity to discuss these results with the clinician. *No treatment decisions should be based on a single test result.* Laboratory errors or false positive results due to interactions with other substances are not uncommon. False positive urine immunoassay tests have been reported for cannabinoids in patients receiving proton pump inhibitors, such as pantoprazole.[12] However, a confirmatory test such as GC/MS will not verify the positive immunoassay result. It is also important to remember that certain benzodiazepines, such as clonazepam, synthetic opioids, such as methadone and oxycodone, are not detected by all immunoassays tests. Those must be specifically requested when ordering a UDT.

Since the UDT is done for the patient's benefit, abnormal results should not be used to force patients out of treatment. Reports indicating substance abuse should signal the need for a medical review of medication dosage and for intensification of counseling and education. However, persistent abnormal results (use of other opioids and other substances, or the lack of the prescribed opioid in the UDS) should generate a review of a patient's opioid treatment and may require referral to a substance abuse specialist.

Summary

Urine testing is a practical, inexpensive, and valuable tool in general medical practice for patient guidance, treatment planning, and dosage determination in opioid-treated chronic pain patients. (Table 2) However, UDTs are under-utilized in clinical practice. In a recent survey among 248 primary care practitioners, only 6.9 % reported obtaining this test before prescribing opioids and only 15 % performed urine toxicology tests on patients already prescribed opioids. [4] Since the UDT is mainly done for the benefit of the patient, the test results should not be the only means to detect substance abuse or monitor treatment compliance. Katz et al suggested that behavioral monitoring and UDTs for patients receiving chronic opioids creates a more comprehensive monitoring system than either alone. [2] Inappropriate testing and overreliance on laboratory results would detract from the clinical management of and damage the clinical relationship with the patient. Therefore, training and education about the benefits and limitations of drug tests are essential to help staff members understand the importance of using test reports appropriately. This would also help the practitioners' concerns of iatrogenic addiction or relapse of previously addicted patients.

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Tahir Tellioglu, MD, is Director, Substance Abuse Division, Rhode Island Hospital, and Assistant Professor of Psychiatry, Warren Alpert Medical School of Brown University.

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Correspondence

Tahir Tellioglu, MD
Rhode Island Hospital Dept Psychiatry
APC 608-B
593 Eddy St.
Providence, RI 02903
e-mail: ttellioglu@lifespan.org

The Creative Clinican

Recurring Meningitis: Recurrence After Suppressive Therapy—Can We Call for Life-long Prophylaxis?

Venkataraman Munusamy, MD, Melissa Nothnagle, MD, and Najam Zaidi, MD

Mollaret's meningitis is a form of recurrent benign lymphocytic meningitis characterized by recurrent episodes of fever and meningismus that resolve without treatment.[1] Though it is most commonly associated with herpes simplex virus (HSV) type 2,[2] rare cases have been attributed to HSV-1,[3] Epstein-Barr virus[4] and other infectious or inflammatory conditions.

Case Report

A 44-year-old female with a history of asthma, depression, irritable bowel syndrome, hypothyroidism, and recurrent meningitis presented to the emergency department of Memorial Hospital of Rhode Island in August 2007 with several hours of headache, nausea, vomiting, fever, neck stiffness and generalized muscle aches. She had no other neurological, urinary, cardiac, respiratory, gastrointestinal or dermatologic symptoms. She denied any recent outbreak of herpes vaginalis or labialis. Her medications included albuterol, levothyroxine and sertraline. She declined any recent use of antibiotics. She had been in a monogamous relationship for the past ten years.

On exam she had a temperature of 100.2° F and a positive Kernig's sign. Fundoscopic exam was normal. Skin, oral, genital mucosa, joints and extremities were normal. Cerebrospinal fluid analysis (Table 1]) showed pleocytosis with a predominance of lymphocytes. Cerebrospinal fluid PCR was positive for HSV-2 Glycoprotein G gene. CT of the brain was normal except for asymmetry in the region of the quadrigeminal plate system in the cerebellar vermis. This is likely a congenital abnormality rather than an epidermoid cyst, rarely implicated in recurrent meningitis.

The patient reported five prior episodes of aseptic meningitis, in 1987, 1990, 1992, 2000 and 2003. In 1987, she had an outbreak of herpes vaginalis, followed a few weeks later by the first episode of aseptic meningitis. The 1992 episode was preceded by herpes labialis, the 2000 episode by herpes vaginalis. She had no herpetic lesions with any of the other episodes. We obtained records from her 2003 hospitalization, at which time CSF- PCR was negative for HSV-1 and 2, and she was treated empirically with intravenous ceftriaxone and acyclovir. Ceftriaxone was stopped after the CSF was culture-negative for 48 hours. Although the CSF-PCR did not detect viral DNA, the episode was diagnosed clinically as recurrent HSV meningitis. She received intravenous acyclovir 750 mg three times a day for two days, to which she responded readily. This was followed by oral valacyclovir, 1 gram every 12 hours, to complete the 14 day course. The patient was discharged on valacyclovir prophylaxis 1 gram PO once daily for a year, as suppressive therapy to prevent recurrence. Early in therapy, valacyclovir was changed to acyclovir, due to abdominal pain and increased cost. She completed her suppressive therapy in March 2004. The patient was not tested for the asymptomatic virus shedding between episodes.

During the current episode, the patient was treated empirically with intravenous acyclovir 800 mg thrice daily; this resulted in rapid relief of headache and resolution of fever. After two days this was changed to oral valacyclovir 1 gram every 12 hours to complete a 14-day course of antiviral treatment. We advised the patient that valacyclovir would be the best choice for subsequent suppressive therapy, due to its greater bioavailability compared with acyclovir; however, given her history of side effects with valacyclovir, she opted for suppression with acyclovir.

Discussion

A large number of cases of Mollaret's meningitis have been reported, and some authors speculate that the incidence might increase. When new HSV-2 infection occurs in the absence of HSV-1 antibodies, higher rates of complications and recurrences are noted.[5] In light of decreasing HSV-1 seroprevalence in the United Kingdom[6] and other developed countries, Davies and colleagues suggest that patients in these areas will be more likely to develop complications of HSV-2 such as recurrent meningitis.[7] Although the exact cause of recurrent episodes of HSV-associated meningitis is unknown, Sato and colleagues have suggested a low immune response secondary to immune evasion by HSV-2 as a possible mechanism.[8]

When Mollaret's meningitis occurs frequently, it can be

Table 1. CSF-Analysis

Year	Biochemical analysis		Cell analysis			Gram stain/ cultures	PCR
	Glucose mg/dl	Protein mg/dl	RBC/ mm^3	WBC/ mm^3	Lymphs %	Gram stain, Lyme IgG, IgM, Cryptococcus, Bacterial/Viral Culture	HSV 2 Glycoprotein G gene
2003	47	52	7	333	87	Negative	Negative
2007	49	109	9	312	71	Negative	Positive

Table 2. Drug Cost and Dosage[16]

Drug	Suppressive therapy dose	Approximate cost per month (US dollars)
Acyclovir	400 mg twice daily	$28.99
Valacyclovir	1000 mg once daily	$337.40
Famciclovir	250 mg twice daily	$199.98

mistaken for chronic meningitis, resulting in multiple hospitalizations with extensive diagnostic testing before establishing a definite diagnosis. Depending on the severity of the patient's illness, length of hospitalization may range from 3 to 15 days, with charges estimated to be $6000.[9] With improvement in the sensitivity of PCR and its decreasing cost, early PCR has a key role in the management of patients with recurrent aseptic meningitis.[10] In addition to preventing excessive testing and repeat hospitalizations, early diagnosis with PCR can facilitate focused management with oral valacyclovir, instead of IV acyclovir, the current customary practice.[11] We propose this in light of evidence from a randomized controlled trial which suggests that the bioavailability of high dose oral valacyclovir is comparable to the levels achieved with IV acyclovir.[12,13] The decision of whether to treat on an outpatient basis or a short inpatient stay is best left to the physician's assessment of individual cases. Oral antiviral therapy might also be beneficial in cases that are preceded by herpes labialis or vaginalis.[10]

In our patient, the sixth recurrence occurred two years after completion of 12 months of suppressive antiviral therapy. Some authors have noted a decrease in the frequency of attacks of recurrent aseptic meningitis with prophylactic antiviral therapy,[14] but no study has been done to demonstrate whether it can prevent recurrence altogether. The failure of suppressive therapy in our case could be attributed to acyclovir's decreased bioavailability only, given the fact that the patient assured compliance to the prescribed suppressive regimen.

A comprehensive literature search found no reports of recurrence of Mollaret's after suppressive therapy. For our patient the current treatment options would be starting antiviral medications at the sign of first meningitis attack or long-term/life-long suppressive therapy. The duration of suppressive therapy in patients with recurrences after suppressive therapy is yet to be studied and formulated.

Physicians must consider cost, side effects, and dosing schedule of antivirals to ensure optimal adherence to the prophylactic regimen.[15] (Table 2) Given that our patient had recurrences approximately every three years, continuous prophylaxis may have been cost-effective if it prevented repeated hospitalizations for each episode.[9] Though Mollaret's meningitis is uncommon, thoughtful management of recurrent attacks with early PCR and long-term antiviral prophylaxis may help patients avoid costly workups and recurrent hospitalizations.

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Venkataraman Munusamy, MD, is a 2nd year resident, Department of Family Medicine, Warren Alpert Medical School of Brown University.

Melissa Nothnagle, MD, is Assistant Professor, Department of Family Medicine, Warren Alpert Medical School of Brown University.

Najam Zaidi, MD, is an infectious disease specialist in the Department of Internal Medicine, Kent County Hospital.

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Correspondence

Venkataraman Munusamy, MD
Department of Family Medicine
Memorial Hospital of Rhode Island
111 Brewster St
Pawtucket, RI 02860
Phone: (401) 729-2204
e-mail: 04venkat@gmail.com

The Warren Alpert Medical School of Brown University
Brown
Division of Geriatrics
Department of Medicine

GERIATRICS FOR THE PRACTICING PHYSICIAN

QUALITY PARTNERS OF RHODE ISLAND
Quality Partners of RI
EDITED BY ANA TUYA FULTON, MD

Successful Interventions for Avoiding Readmission In the Elderly

Rebekah L. Gardner, MD

For an elderly patient, hospitalization can herald a cascade of admissions and progressive functional decline. Readmissions, often defined as those that occur within a specified time frame after discharge from an index admission, are particularly frequent among patients initially admitted with congestive heart failure, chronic obstructive pulmonary disease, myocardial infarction, diabetes, and stroke. In addition to the deleterious effects of the hospitalization itself, the act of transferring patients back and forth between healthcare settings creates an opportunity for medical errors and miscommunication.[1] With shorter hospital stays and an increasing prevalence of hospitalists, the discharge transition is fraught for elderly patients with multiple chronic conditions. Healthcare staff may relay information about patients' medical histories, medications and allergies, and prior testing late, incorrectly, incompletely, or not at all. This transition gap is receiving recognition at all levels of patient care delivery, and the Centers for Medicare & Medicaid Services has targeted care transitions and hospital readmissions as areas needing quality improvement. More and more, rates of readmission to the hospital are perceived as markers for quality of care.[2]

Over the last fifteen years, investigators have undertaken a variety of studies to understand why particular diseases and patient subgroups are at higher risk for readmission. They have proposed different interventions to ameliorate the transition from the hospital. Unfortunately, it is difficult to know what works. Categorizing the possible interventions is challenging because of marked heterogeneity in every aspect of the effort. For example, some investigators begin when patients are first admitted, while others focus on patients' arrival at their first post-discharge clinic visit. More ambitious programs seek to pursue change at multiple points between admission and discharge. This article will discuss some of the more successful interventions.

Pre-discharge interventions

Many interventions target patients while they are still in the hospital. Patients may be assessed for risk of poor outcomes, educated about their condition, trained on self-management skills, evaluated by geriatric consultants, or given follow-up appointments before leaving the hospital. Interventions often include the patients' caregivers in the patient education and discharge planning.

Koelling and colleagues provide an example of a successful pre-discharge intervention in patients admitted with congestive heart failure.[3] The researchers compared standard discharge care with the addition of a one-hour, one-on-one teaching session with a nurse educator. The session focused on the principles of heart failure and the rationale for therapy, dietary recommendations, and self-management strategies. With this intervention, they halved heart failure readmissions within 180 days of discharge.

Post-discharge interventions

The majority of transition interventions in the literature take place after hospital discharge. Typically these incorporate a home visit, often by an advanced practice or specially trained nurse. Depending on the study, a variety of medical personnel (physicians, pharmacists, physical therapists) might also perform patient assessments, measure vital signs, and make management recommendations. In addition to patient visits and recommendations, providers also perform medication reconciliation, educate patients and their caregivers, facilitate communication with patients' primary care physician or specialists, or work on self-management skills.

Disease management programs often provide the framework for this approach. Young and colleagues found that in patients discharged after myocardial infarction they reduced readmissions by about half by using a protocol that included six home visits by a nurse trained in cardiac care, a standardized assessment checklist, communication with primary care physicians, and patient education.[4]

Telehealth interventions

Telehealth interventions are an emerging strategy to prevent readmissions. This category represents a variation of post-discharge home care intervention, but instead of a nurse visiting patients' homes, the assessment and communication occur remotely, usually by telephone. These programs range from unstructured telephone calls to multiple calls with the goal of teaching self-management skills, promoting medication adherence, and adjusting therapies based on symptoms. Other interventions provide in-home instruments to allow daily measurement of weight, blood pressure, heart rate, and rhythm, which patients then transmit over a telephone line.

One successful telehealth intervention included three months of remote monitoring of patients with angina and congestive heart failure.[5] The program included weekly video conferencing to assess patients' progress and to provide education; blood pressure and weight were transmitted daily over a

telephone line. The investigators reduced readmissions by a third during this period, with much of the benefit in the patients with angina. A systematic review of home monitoring for patients with heart failure reported a positive impact on hospital readmissions, as well as emergency department visits and quality of life.[6]

Multidimensional interventions

Multidisciplinary, multidimensional interventions address several points along the patient pathway and incorporate many of the modalities discussed above. These are often intensive, both in time and resources; and almost all include advanced practice nurses. In one of the best-known studies in this category in older patients with congestive heart failure, Naylor and colleagues reduced readmissions by a third.[7] Specially trained nurses visited patients within 24 hours of their index hospital admission and then daily while the patients were hospitalized. They performed a comprehensive assessment of patients and caregivers, spearheaded discharge planning, coordinated care among the patients' hospital and outpatient physicians, and assisted with medication regimens. They then performed a home visit within 24 hours of discharge and weekly for the first month. The nurses were also available by telephone 7 days a week.

Coleman's group also demonstrated a substantial decrease in readmissions by incorporating an advanced practice nurse in a multidimensional intervention.[8] Similar to Naylor's study, the nurse met with patients while they were in the hospital, made home visits, and helped patients manage their medications. In Coleman's work, however, the nurse acted as a "coach" for patients and their caregivers; nurses did not participate in medical management and were not involved as another healthcare provider. For example, the nurse encouraged the patients to call their primary care physician if questions arose and rehearsed the upcoming encounter to help patients articulate their needs.

Challenges in the field

Judging the generalizability of a particular intervention is challenging. Successful transition interventions may rely on one or two specific nurses or may address a shortcoming in a particular delivery network. In addition, much of the research is coming from abroad, and different health care systems, particularly single-payer systems, may produce different outcomes than a similar intervention in the United States. Many of the interventions that appear to work in one study will show no significant effect in another. Some discharge interventions have actually been associated with an increase in readmission rates.[9]

Additionally, the studies vary in the duration of the intervention, and in the frequency and intensity of patient contact. The measured endpoints vary from study to study. Although this discussion focuses on readmissions, studies also examine other clinical factors (e.g., mortality, medication use, guideline adherence, and functional status), healthcare utilization (e.g., days in hospital when readmitted, multiple readmissions, emergency department visits, and total costs), knowledge of disease management, quality of life, patient satisfaction, and caregiver burden. Lastly, the number of patients included in each study is often small, and projects may be underpowered to detect meaningful results. Although researchers have performed systematic reviews and meta-analyses to capture these effects, the results are often equivocal.

Successful elements

Most systematic reviews of these transition interventions cautiously report some evidence of their efficacy.[10] Interventions that include both a pre-discharge and a post-discharge component and interventions that include some aspect of patient education and self-management seem to be the most beneficial.[11] Early post-discharge involvement and frequent contact also have been cited as important elements in improving clinical outcomes.[12]

Encouragingly, almost all interventions which measure cost show a decreased cost associated with performing the intervention, regardless of whether the number of readmissions had been reduced. This is because often investigators are able to demonstrate a decrease in the number of days patients stay in the hospital when readmitted or a decrease in "multiple readmissions." Cost-effectiveness is a particularly compelling outcome when investigators include *total* healthcare costs in their calculations, not just hospital costs. Ironically, despite the benefits and likely cost-effectiveness, hospitals may actually profit from readmissions. Consequently, It may be reasonable to target health insurers as potential sponsors and to emphasize the link to quality of care to create incentive in reluctant participants.

Upcoming Demonstrations

The **Centers for Medicare & Medicaid Services** (CMS) have focused on care transitions in their 9th Scope of Work for quality improvement. In the coming months, they will select 18 states to create demonstration projects aimed at reducing readmission rates. These interventions will address system-level weaknesses, specific diseases that carry high risk of readmission, and drivers of local readmission rates.

Conclusion

Readmissions after a hospitalization are common in the elderly, and certain diseases, such as congestive heart failure, are associated with a particularly high readmission rate. There is an enticing array of potential interventions to ameliorate this problem - from a simple telephone call after discharge to a multidisciplinary, multidimensional year-long intervention - and many appear promising in reducing readmissions and lowering costs. Future research should attempt to standardize intervention taxonomy, design, and outcome measures to facilitate comparison across multiple protocols. In addition, more investigation is required to determine which aspects of the multidimensional interventions are the most effective.

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Rebekah L. Gardner, MD, is Assistant Professor of Medicine, The Warren Alpert School of Medicine of Brown University, and Senior Medical Scientist, Quality Partners of Rhode Island.

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Rapids

by Louise Giguere

Like a river, the natural flow of life
the source, what force, the majesty,
the depth, making its mark, surrounds,
the edges, its determined course,
profound.

It turns, it bends, smooth as glass,
a willowy reed, like an innocent lass,
lulled, to the sound of motion, floating,
mellowed, unaware of the gradual change.

The range, the increasing turbulence,
the broken sound, the uneven obstructions
not budging, but judging, the current of breath,
the forecast, the charge, the venous protest

The slow boil fury of cold foam,
oscillates, blinding,
rapt, treasonous tears
It's calling.

The aqueous energy stirred,
straight through.
delving deep, deeper, the unfamiliar,
the rapids they were.

Cresting, the rapid phase, leveling,
the waters calmed, gently flowing,
recalling, the feelings,
the squalor of reversing tides,
on its way.

The birth, the stream, the flexing range,
fountain head fluxes, forward,
to the great somewhere.

The rapids remembered, like a river felt,
life's blood, the natural flow of life,
navigating, nearing the source, wending,
wild and winsome, the greatest course,

Rapids, once again, surrenders.
To be, the current, the force,

The open seas

The author, who lives in Coventry, has written this poem around her stroke. She writes: "'Rapids' is a metaphor about a mindset and emotional well being, while paralleling the assault on the blood vessels leading to the actual stroke experience. The poem continues with recognition, acceptance, change, and finally ongoing emotional and physical recovery."

CORRESPONDENCE:
Louise Giguere
e-mail: Lougig579@yahoo.com

Circumstances of Suicide Death in Rhode Island 2004-2006

Wendy Verhoek-Oftedahl, PhD, Edward F. Donnelly, RN, MPH, Miriam Fenton, and Thomas Gilson, MD

Suicide has been identified as one of three top injury prevention priorities in Rhode Island (RI).[1] In **2005** suicide was among the five leading causes of death for all people in the US age 10 to 54 years as well as for RI residents in this age group.[2] Circumstances of suicide deaths have not been well studied in RI, missing an important opportunity for prevention. In 2003 the **Centers for Disease Control and Prevention (CDC)** funded Rhode Island to participate in the **National Violent Death Reporting System (NVDRS)**, a surveillance program for intentional injury deaths.[3] The NVDRS collects detailed demographic and circumstance data on homicides, suicides, deaths of undetermined intent, and unintentional firearms deaths according to standardized procedures and protocols. Currently, 17 states are participating. The **Rhode Island (RI)**, component known as the **RI Violent Death Reporting System (RIVDRS)**, began data collection in 2004. This is the first detailed report of suicide circumstances based on RIVDRS data.

Methods

Data on suicide deaths that occurred in RI from 2004-2006 were extracted from RIVDRS. RIVDRS contains information on decedent demographics, autopsy and toxicology results, and life circumstances abstracted from medical examiner and hospital records, death certificates and police reports. These reports are routinely collected under the jurisdiction of the RI Office of State Medical Examiners. Cases are identified by review of deaths entered daily in the Medical Examiner Log. RIVDRS staff abstract and enter data into NVDRS database software according to CDC procedures and protocols. Data collection for most cases is complete within six months of the death.

Analysis was conducted using SPSS version 14.0. Rates of deaths per 100,000 population were calculated using population estimates for Rhode Island as of July 1, 2008, from the US Bureau of the Census.[4]

Results

Two hundred fifty-eight suicide deaths occurred in Rhode Island between January 1, 2004 and December 31, 2006. Suicide deaths were highest among men, whites and individuals age 50-59, as were rates (not shown). (Figure 1)

Circumstances were known for 255 of 258 decedents (98.8%). Where known, the most frequent circumstances reported were associated with mental health: 62.7% of decedents were reported to be experiencing current mental health problems with 51.8% reported to be receiving current mental health treatment. While 48% of males and females were reportedly depressed, 40.6% of males were reported to have a diagnosis of depression compared with 51.7% of females. (Table 1) The most frequent life circumstances reported were: a crisis within two weeks prior to the suicide (33.3%), an intimate partner problem (30.2%), and an alcohol or substance abuse problem (29.4%). The proportion of males reported to be experiencing these problems was higher than the proportion of females.

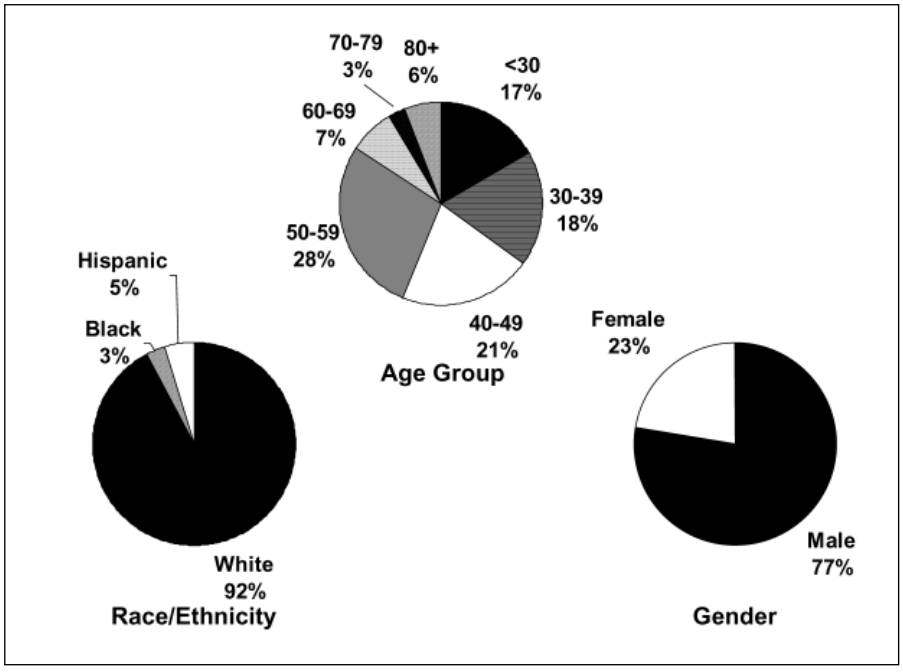

Figure 1: Percentage Distribution of Suicides by Age, Race/Ethnicity and Gender, Rhode Island 2004-2006.

Differences in suicide circumstances by age of decedent were also observed. (Table 2) While close to 50% of decedents across age groups were reported to be in a depressed mood, a smaller proportion of victims age 13-34 than older victims were reported to have had a current mental health problem and to have a diagnosis of depression. A higher proportion of victims age 13 to 34 years had experienced a recent crisis while a higher proportion of victims age 65 years and older were reported to have had a physical health problem. Higher proportions of younger decedents (<65 years) were reported to have had intimate partner problems and alcohol or substance abuse problems.

Table 1. Suicide Circumstances by Sex, Rhode Island 2004-2006

MOST FREQUENT CHARACTERISTICS	Male		Female		Total	
	No	%	No	%	No	%
Current depressed mood	94	47.7	28	48.3	122	47.8
Current mental health problem	115	58.4	45	77.6	160	62.7
Current mental health treatment	96	48.7	36	62.1	132	51.8
Diagnosis of depression	80	40.6	30	51.7	110	43.1
Ever mental health treatment	107	54.3	41	70.7	148	58.0
Crisis within 2 weeks of the suicide	73	37.1	12	20.7	85	33.3
Physical health problem	46	23.7	16	27.6	62	24.3
Left a suicide note	80	40.6	27	46.6	107	42.0
Intimate partner problem	62	31.5	15	25.9	77	30.2
Alcohol or substance abuse problem	62	31.5	13	22.4	75	29.4
History of suicide attempts	41	20.8	21	36.2	62	24.3
Disclosed intent to commit suicide	63	32.0	19	32.8	82	32.2

Table 2. Suicide Circumstances by Age, Rhode Island 2004-2006

MOST FREQUENT CIRCUMSTANCES	13 to 34 years		35 to 64 years		65 years and older	
	No.	% in age	No	% in age	No	% in age
Current depressed mood	28	46.7	78	47.9	16	50.0
Current mental health problem	32	53.3	108	66.3	20	62.5
Current mental health treatment	26	43.3	91	55.8	15	46.9
Diagnosis of depression	19	31.7	76	46.6	15	46.9
Ever mental health treatment	33	55.0	98	60.1	17	53.1
Crisis within 2 weeks of the suicide	33	55.0	45	27.6	7	21.9
Physical health problem	5	8.3	35	21.5	22	68.8
Left a suicide note	20	33.3	73	44.8	14	43.8
Intimate partner problem	21	35.0	54	33.1	<5	--
Alcohol or substance abuse problem	13	21.7	62	38.0	0	0.0
History of suicide attempts	12	20.0	44	27.0	6	18.8
Disclosed intent to commit suicide	22	36.7	49	30.1	11	34.4

Discussion

RIVDRS data reveal important age and sex differences that can inform prevention efforts. Nationally, the highest rates of suicide are observed among older individuals although rates in middle-age males have been increasing since 1999.[2,5] In contrast, in RI the highest rate of suicide was observed for individuals age 50-59; therefore, prevention efforts in RI should target this population. RIVDRS circumstance data indicate that mental health problems may be under-recognized and under-treated, particularly among males and persons less than age 35. In addition persons experiencing life crises, intimate partner problems, and substance abuse problems, particularly males and younger individuals, appear to be at increased risk of suicide while older individuals with physical health problems also appear to be at increased risk.

Knowledge of suicide circumstances provides new information on at-risk individuals and can inform the development of more targeted prevention interventions. While middle-age males appear to be at particularly increased risk, this population may be difficult to reach. Physicians can assist in this effort by using patient visits for episodic and routine care to identify and refer patients potentially at-risk for assessment and treatment.

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Wendy Verhoek-Oftedahl, PhD, is Assistant Professor of Community Health (Research), Warren Alpert Medical School of Brown University.

Edward F. Donnelly, RN, MPH, is Senior Public Health Epidemiologist, Center for Health Data and Analysis, and Clinical Teaching Associate, Department of Community Health, Warren Alpert Medical School of Brown University.

Miriam Fenton is an MPH Candidate, Brown Program in Public Health, Warren Alpert Medical School of Brown University.

Thomas P. Gilson, MD, is Chief Medical Examiner and Clinical Assistant Professor of Pathology and Laboratory Medicine, Warren Alpert Medical School of Brown University.

Tuberculosis Outbreak In a Rhode Island High School

John P. Fulton, PhD, Utpala Bandy, MD, MPH, Michael Gosciminski, MT, MPH, Carol Browning, MS, RN, BC, Christine Goulette, MS

In January 2008, a case of active infectious tuberculosis (TB) was reported to the Center for Epidemiology and Infectious Diseases at the **Rhode Island Department of Health (HEALTH).** Control measures put in place included home quarantine and treatment of the index case (using daily observed therapy) and extensive evaluation of all persons exposed to the index case in school and non-school settings. The investigation revealed a secondary case of active infectious TB in the school linked conclusively to the index case. No other active cases were documented as part of this outbreak.

TB is a bacterial infection of the lungs, which is transmitted through the air-borne route from infectious droplets expelled from the lungs during coughing, sneezing etc. The standard method for detecting TB infection is by performing a **tuberculin skin test (TST),** by injecting a small amount of "**Purified Protein Derivative" (PPD)** into the forearm, and observing the reaction. The test needs to be repeated 8-10 weeks after the baseline test, as "conversion" (an indicator of development of immunity after infection) is a slow process. TB develops after acquiring infection in two forms, active TB (which can be infectious and symptomatic), and much more commonly, a latent form (called **latent TB infection or LTBI**) where the germs are contained in the body in a dormant or "latent" capacity and the person feels well; individuals with latent TB infection are not infectious; the only indication of infection usually is a positive TST. LTBI has the potential of becoming active (10% overall lifetime risk), so should be treated as well. Both forms of TB can be treated with regimens of anti-tuberculosis antibiotics.[1]

CASES AND CONTACT INVESTIGATION

The index patient, a 17 year old 11th grader, was symptomatic with cough, fever, and a 10 pound weight loss during the 10 weeks preceding diagnosis, and continued to attend school and work at an after school job while infectious. A chest radiograph, TST, and sputum examination all confirmed infectious active TB. Thus the risk of exposure among immediate family members, close friends, and co-workers was considered high. The risk of exposure to classmates, other student contacts, and staff at the high school was also high. The patient was placed on treatment for active TB and quarantined at home until non-infectious. An immediate contact investigation and intense case finding process was undertaken, in accordance with CDC guidelines.[2]

Table 1 - Frequencies

Testing Category	Students	Staff	Total
Prior Positives	66	3	69
Baseline Positives	40	6	46
Conversions (Attributable to Case 1 or 2)	18	2	20
Conversions (Attributable to Case 2)	7	0	7
Negatives	616	100	716
Partially Evaluated	59	28	87
Not Evaluated	145	8	153
Total	**951**	**147**	**1098**

HEALTH immediately initiated skin testing for TB among all close community and household contacts identified in the course of the ongoing investigation. Additionally, skin testing was initiated at the high school with a recommendation that all classmates of the patient, all additional students in grades 11 and 12, and all staff be tested. HEALTH tested all eligibles twice, once in January, to establish baseline reactions to the test, and again in March, to identify possible "conversions" from negative to positive skin test results, as an indicator of newly acquired infection. As expected, several students and members of the school staff either gave a history of positivity to previous TB tests or tested positive at baseline, in January 2008. All such individuals who had not been diagnosed and treated previously for LTBI received referral to the state-supported RISE TB Specialty Clinic affiliated with the Miriam Hospital in Providence for full medical evaluation and treatment.

In March a second round of testing was conducted. Several skin test conversions were identified among students and staff, and these individuals were referred to the TB Clinic for medical work-up and treatment. All conversions except one student, an 11th grade female, were diagnosed with LTBI. The 11th grader was diagnosed with active, infectious TB on the basis of positive chest radiograph and positive sputum results. The student was placed on a medication regimen for active TB and was quarantined at home until non-infectious. Subsequent investigation revealed a close social connection between the first and second infectious patients. Additional genotyping results showed a spoligotype and MIRU (mycobacterial interspersed repetitive units) result that matched the index patient's isolate but no other isolate recorded in the **National TB Genotyping Service (NTGS)** database of over 35,000 isolates, thus confirming that the first patient was the most probable source of infection for the second.

Because the second infectious 11th grader may also have exposed others at the high school, HEALTH conducted a third round of testing in June (8-10 weeks after last exposure to the second case), this time inviting students in all grades and all staff in the school to receive TSTs. At this time, additional individuals not previously screened were identified as having histories of positive TSTs for TB (prior positives). Others tested positive for the first time in June. Several of the latter were considered "conversions" from previous negative test results in January, in March, or both; the rest were considered "baseline positives." All such individuals were referred to the RISE TB Clinic for medical work-up and treatment. None were found to be infectious, i.e., none were found to have active TB.

Table 2 - Rates

Testing Category		Rate
Students		
Background Positivity:	(66+40)/ 806	13%
Conversions (Case 1&/or 2):	(18)/ 679	3%
Conversions (Case 2):	(7)/ 623	1%
Staff		
Background Positivity:	(3+6)/139	6%
Conversions (Case 1&/or 2)	(2)/108	2%
Conversions (Case 2):	(0)/100	0%

Results of Contact Investigation: Students

In the course of three rounds of TB testing, HEALTH attempted to evaluate 951 students. HEALTH was unable to test 145 in any of the three rounds, because of absenteeism, suspension from school, or election not to be tested. Another 59 were tested in rounds one or two but not in round three. (Table 1). Given possible exposure to the second infectious patient, students not evaluated in round three are considered not to be fully evaluated. HEALTH and school officials have made every attempt to reach these students thus far, and continue active surveillance with the goal of full evaluation of all students potentially exposed to active infectious TB. (Neither the state nor the CDC recommends that asymptomatic individuals—students or staff members—be excluded from school.)

616 students tested negative in the third round of testing, and were therefore considered negative for TB (negative for LTBI and negative for infectious TB). In all, 131 of the 806 students tested at least once had positive test results. Of these students, 66 reported prior positive skin tests (prior positives), and 40 had positive test results when first tested at the high school (baseline positives). Baseline testing of students occurred in round one (January) as well as round three (June).

25 students tested negative in one round of testing (rounds one or two), then positive in a subsequent round of testing (rounds two or three), and therefore were considered conversions. Given the timing of testing (and because the infectious periods of the two cases overlapped), 18 of the 25 students may have converted because of exposure either to the first and/or to the second infectious case. Another seven may have converted because of exposure to the second infectious case, but not to the first. These students were recorded negative 8-10 weeks after exposure to the first case, but converted subsequently. Given two infectious cases in a densely populated congregate setting, it is likely that most of the recorded conversions were related to recent exposure, but a small, undetermined number of conversions may also be explained in one of two ways: a) recent exposure to another infectious case outside the high school, (for example while visiting in a highly endemic country for more than 4 weeks—a few "converters" gave such a history); or b) LTBI acquired in early childhood, where the skin test intensity wanes to become negative on initial testing, but subsequent, positive reactions are stimulated by the first test - phenomenon called "boosting."

The numbers of prior positives, baseline positives, and conversions may be reduced to rates by carefully constructing denominators from the number of students who were tested successfully in different rounds. (Table 2).

- **Background positivity:** 13% of students tested positive, either prior to testing at the high school or upon first being tested at the high school.
- **Conversions linked to cases 1 or 2:** 3% of students converted in the second or third round of testing, after testing negative in the first round. These conversions may be attributed to either of the two infectious cases.
- **Conversions linked to case 2 alone:** 1% of students converted in the third round of testing, after testing negative on the second round. These conversions may be attributed to the second infectious case (but not to the first infectious case).

Results of Contact Investigation: Staff

In the course of three rounds of TB skin testing, HEALTH attempted to test 147 staff members, including faculty, administrative staff, cafeteria staff, and custodial staff. HEALTH was unable to test a total of eight in any of the three rounds, because of election not to be tested. Another 36 staff members were tested in rounds one or two but not in round three (See Table 1). Given possible exposure to the second infectious patient, staff members not evaluated in round three are considered not to be fully evaluated. To date, HEALTH and school officials have made every attempt to convince staff members to be fully evaluated, and continue to do so with the goal of full evaluation of all staff members potentially exposed to active infectious TB.

100 of the staff tested negative on the third round of testing, and were thus considered negative for TB (negative for LTBI and negative for infectious TB). In all, 11 of 139 staff members tested at least once had positive test results. Of these, three reported prior positive TSTs ("prior positives"), and six tested positive on first testing at the high school ("baseline positives"). Baseline testing of staff members occurred in round one (January) as well as round three (June). Two staff members tested negative in one round of testing, then positive in a subsequent testing, and therefore are considered "conversions." Because of the timing of the tests, the two conversions among staff members may be attributable either to the first or to the second infectious case.

The numbers of prior positives, baseline positives, and conversions may be reduced to rates by carefully constructing denominators from the number of staff members who were tested successfully in different rounds (Table 2).

- **Background positivity:** 6% of staff members tested positive either prior to testing at the high school or upon first being tested at the high school.
- **Conversions attributed to cases 1 and/or 2:** 2% of staff members converted in the second or third rounds of testing, after testing negative in the first round. These conversions may be attributed to either of the two infectious cases.
- **Conversions attributed to case 2 alone:** None.

Medical Referral and Case Management

All persons evaluated with a positive TB skin test on any of the three rounds of testing (including prior positives, baseline positives, and conversions) were referred to the state-supported Rise TB Specialty Clinic affiliated with the Miriam Hospital for follow-up evaluation, diagnosis, and treatment. Typically, a patient thus referred is

questioned carefully to develop a comprehensive family, social, and illness history. After full medical evaluation and diagnosis, patients are prescribed medication regimens for their LTBI or active disease. Patients are followed closely throughout this period to assure strict adherence with therapy and completion of therapy. As the period of therapy is several months, regular follow-up medical care and counseling is important in TB case management. Less-than-strict adherence to drug regimens can result in the development of drug-resistant organisms which are very difficult to cure and increase the risk of prolonged infection and death, both for active disease and LTBI, should reactivation occur.

Lessons Learned and Recommendations

1. Mass Clinic Operations: Schools are good settings for mass clinic operations in a public health emergency. HEALTH activated **ICS (Incident Command System),** which organized the effort and provided resources far beyond those immediately available from the small TB program at HEALTH. The ICS structure thus fielded included a large operations unit (with branches addressing several areas such as epidemiology, school testing clinic, laboratory etc.), assisted by legal, financial, logistics, planning, safety, and communications units. The three mass TB skin testing clinics at the school ran efficiently, staffed by a team of professionals from HEALTH, the high school, the RISE TB clinic, and **Rhode Island's Disaster Medical Assistance Team (RI DMAT)**. Clinic team members, led by a TB program nurse, worked closely with one another to effect rapid and efficient processing of students and faculty. As well, a Public Health Advisor assigned by request from the Division of TB Elimination at the **Centers for Disease Control and Prevention (CDC)** provided valuable assistance with the third (final) testing round at the high school, tracking down difficult-to-find high risk contacts in the community, as well as providing guidance and assistance with the in-school screening itself. The smoothness of the operation engendered confidence in students and staff members, and undoubtedly among parents as well, who were kept regularly updated through meetings at the school about the progress of screenings in the aggregate, and about the specific test results of their children (by letter), as the latter became available. Staff members of the high school were also updated in separate assemblies so that they could provide appropriate public health messages to students and parents, while allaying their own fears.

2. TB Clinical and Laboratory Resources: The mass testing resulted in the referral of 142 students and staff members to the state-supported TB Clinic for follow-up evaluation, diagnosis, and treatment as necessary. The availability of this specialized resource was directly responsible for the rapid and accurate identification of the second case, leading to early treatment and early quarantine as a control measure, thus preventing an escalation of transmission. The TB Program has a long-standing contractual relationship and a strongly collaborative work relationship with the Miriam Hospital and its state-funded TB Clinic. Maintenance and support of an expert facility to assure response capacity for TB control in routine and outbreak situations such as this one is a critical core function of state government. In the absence of this clinic the control response would have been difficult, and cases of TB may have gone undetected. The clinic is supported by the state mycobacteriology laboratory that houses modern technology capacity for TB laboratory testing, and is a critical arm of TB control as well. The state laboratory serves all clinicians in the state.

3. LTBI prevalence: Data were studied to provide prevalence rates for LTBI by country of origin in this school population. Of note, prior history of a documented TB positive skin test was nine times more common among students born outside the US (18.1%) than those born in the US (2.1%). These numbers are not very different from national estimates of LTBI prevalence among US born and foreign born persons as determined by the National Health and Nutrition Examination Survey (NHANES) 1999-2000.[4] HEALTH now has an excellent cross-sectional view of LTBI prevalence among high school students in one of its most diverse municipalities. The school population is 60% Hispanic, 10% non-Hispanic Black, 16% non-Hispanic white, and 7% Portuguese or Cape Verdean. The baseline and prior LTBI cases hailed from many countries including Guatemala, The Dominican Republic, Colombia, Cape Verde, Mexico, Liberia, and Poland, to name a few. The most important risk factor associated with LTBI is foreign nativity.

The data clearly support American Academy of Pediatrics practice guidelines to perform targeted testing (not universal screening) for TB during prescribed periodic well child visits, especially among the foreign born who are immigrants from countries with high TB disease rates or who travel to such countries for more than four-week stays. Pediatricians are encouraged to perform testing and to ensure completion of LTBI treatment for such children. Universal TB skin testing outside the setting of a medical home is not recommended.[3,5] A commitment to test is generally considered a commitment to treat.

4. TB Control Priorities and Direction: The control and elimination of TB relies on two critical concepts: a) Successful treatment of all infectious cases, and b) prevention of active TB disease by treating LTBI, identified through contact investigations and targeted testing.[1] Mass testing at the school uncovered 24 cases of LTBI (and one active case) related to recent contact with an active case. These are the highest priority contacts for ensuring treatment adherence and completion. They are at highest risk (in the first two years following infection) of progressing to active TB. The 139 individuals who have prior or baseline LTBI (most represent individuals who are candidates for targeted testing based on country of origin) are also priority candidates for LTBI therapy, as adolescence is a prime age group in which LTBI can progress to active TB. Thus, this entire group is a priority group for assuring completion of therapy. Staff of the TB Program at HEALTH, school nurses, and staff of the RISE TB Clinic will continue to track these priority groups to assure completion of therapy in the months to come. This outbreak has burdened all available resources of the small RI TB Program and the RISE TB clinic with a large bolus of patients; therefore, continued support for this public health assurance function of state government is imperative.

Primary care clinical providers must also develop expertise in the performance of targeted testing for LTBI and in the treatment of cases so detected, because the ongoing detection and treatment of LTBI is essential to the prevention of progression to active TB. See http://www.health.ri.gov/disease/communicable/tb/ltbi-resources.php for clinical guidance on treatment of LTBI.

Additionally, LTBI surveillance will be made operational as part of our TB Control strategy in RI beginning in 2009, following proposed revisions to the rules and regulations for the reporting of communicable diseases. Clinical providers will receive guidance on LTBI reporting in the next few months. Trend data on LTBI prevalence, demographics, treatment adherence, and barriers to care will inform future public health policies with regard to community-based LTBI clinical care.

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John P. Fulton, PhD, is Chief Health Program Evaluator, Center for Epidemiology and Infectious Diseases, Rhode Island Department of Health, and Clinical Associate Professor of Community Health, Warren Alpert School of Medicine, Brown University.

Utpala Bandy, MD, MPH, is Assistant Medical Director, Center for Epidemiology and Infectious Diseases, Rhode Island Department of Health, and Clinical Assistant Professor of Community Health, Warren Alpert School of Medicine, Brown University.

Michael Gosciminski, MT, MPH, is Public Health Epidemiologist, Tuberculosis Program, Center for Epidemiology and Infectious Diseases, Rhode Island Department of Health.

Carol Browning, MS, RN, BC is Community Health Nurse Coordinator, Tuberculosis Program, Center for Epidemiology and Infectious Diseases, Rhode Island Department of Health.

Christine Goulette, MS, is Program Manager, Tuberculosis Program, Center for Epidemiology and Infectious Diseases, Rhode Island Department of Health.

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The authors have no financial interests to disclose.

Images In Medicine

Pyogenic Ventriculitis

Antonio Alvarez, MD, and Glenn Tung, MD, FACR

An unresponsive 52 year-old woman was brought to the emergency department. Noncontrast CT of the brain (Figure 1) showed a left frontal mass (arrow) with edema. After open drainage of the pyogenic brain abscess, antimicrobial therapy was begun. MR imaging was performed because of neurologic deterioration. A contrast-enhanced T1-weighted image (Figure 2) shows a small residual rim-enhancing frontal brain abscess (arrow) and linear enhancement of the ependyma in the frontal (notched arrow) and occipital horns (bent arrow) of the left lateral ventricle. A diffusion-weighted MR image (Figure 3) demonstrates hyperintense signal in both the core of the brain abscess (arrow) and in dependent ventricular fluid (bent arrow). Purulent fluid was drained from a ventricular shunt catheter, confirming the diagnosis of pyogenic ventriculitis.

Pyogenic ventriculitis is a rare and potentially lethal cerebral infection that can result from rupture of a brain abscess, extension of meningitis into the ventricles, or a complication of neurosurgery.[1,2] Signs of ventricular empyema on MR imaging include hydrocephalus, abnormal signal in the periventricular white matter, ventricular debris, and ependymal contrast-enhancement.[1] Purulent fluid within the ventricles or in the core of a pyogenic abscess should be suspected when water diffusion is markedly decreased on diffusion-weighted MR imaging, a sign attributed to the high viscosity or presence of inflammatory cells and proteinaceous debris in pus.[1]

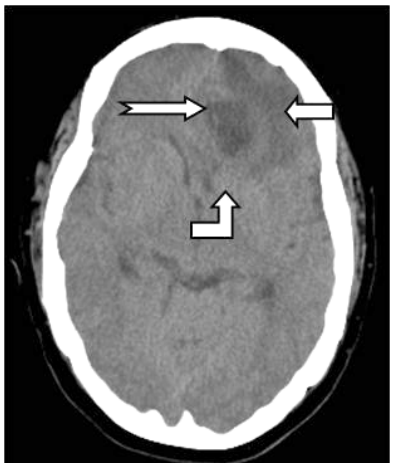

Figure 1.

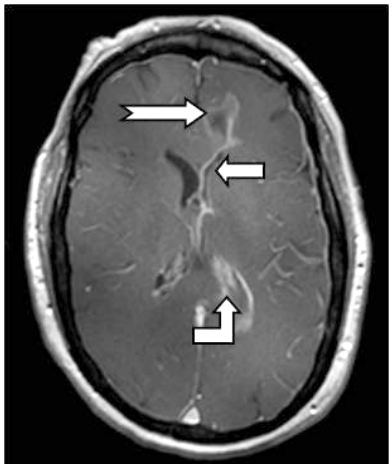

Figure 2.

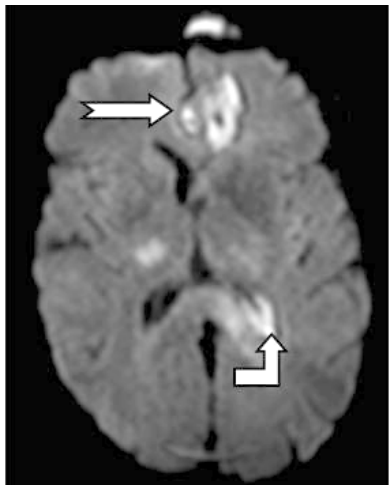

Figure 3.

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Correspondence

Antonio Alvarez, MD
E-mail: aalvarez3@lifespan.org

Antonio Alvarez, MD, PGY3, is a Resident in the Department of Diagnostic Imaging, Rhode Island Hospital and the Warren Alpert Medical School of Brown University.

Glen Tung, MD FACR, is Director of Clinical Research, Department of Diagnostic Imaging, and a member of the Teaching Faculty, Department of Diagnostic Imaging, Neuroradiology, at Rhode Island Hospital and the Warren Alpert Medical School of Brown University.

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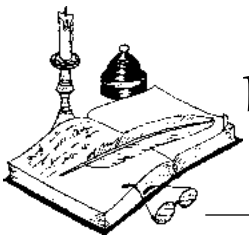

Physician's Lexicon

The Enigmatic Words of the Urinary System

The medical vocabulary of the urinary system, a one-way fluid-conveying entity from renal pelvis to urethra, employs words of both Greco-Roman and Germanic origins, and even ventures hesitantly into early Greek mythology.

The word, kidney, is derived from an older Germanic word meaning egg-like, presumably chosen because of the oval shape of the organ. The Classical adjectival words, *renal* and *nephric*, are derived, respectively, from the Latin, *ren*, and the Greek, *nephros*.

The word, bladder, comes from an Old English word, *blaedre*, meaning blister or sac; and this word, in turn, derives from an older Teutonic word meaning to inflate. The word, cyst [as in cystic, cystitis, cystoscopy] is Greek, meaning a pouch or sac and descends from an earlier Indo-European word meaning to expel or sigh.

Cloaca is from the Latin, *clovaca*, meaning a sewer [and specifically, Rome's major sewer draining into the Tiber river.] The word stems from a Greek word meaning to rinse or drench and is cognate with the Greek root, *clys* - , seen in medical terms such as clyster [a syringe], or clysma [an enema]. The English word, cataclysm [a violent upheaval, a washing out] contains the same root.

Urine, and related words [ureter, urethra] are derived from the Greek, *our*, meaning urine.

The word, sphincter, the muscles controlling egress from the bladder, comes from a Greek word meaning that which strangles or grips. In Greek mythology, a winged monster with a woman's head, a lion's body, a serpent's tail and the wings of an eagle, stood astride the ancient road to Thebes and was called Sphinx [derived from the same Greek root]. The Sphinx confronted Pilgrims on this road and gave them a riddle. If the answer was incorrect, the Sphinx strangled and ate the hapless journeyman. Oedipus, in Greek legends, answered the riddle correctly; and the Sphinx, in frustration, cast herself over a cliff and perished. The family of complex chemicals called the sphingolipids [and derivative words such as sphingolipidosis, sphingosine, sphingomyelin] come from the same Greek root, but they were chosen not to signify strangling, but as a metaphor for mysteriousness or enigmatic, terms often used to describe the Thebes Sphinx.

– Stanley M. Aronson, MD

Rhode Island Department of Health
David Gifford, MD, MPH
Director of Health

Vital Statistics

Edited by Colleen Fontana, State Registrar

Rhode Island Monthly Vital Statistics Report Provisional Occurrence Data from the Division of Vital Records

Underlying Cause of Death	Reporting Period			
	September 2007	12 Months Ending with September 2007		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	194	2,724	254.6	3,894.0
Malignant Neoplasms	158	2,251	210.4	5,730.0
Cerebrovascular Diseases	28	393	36.7	614.5
Injuries (Accidents/Suicide/Homicde)	44	546	51.0	8,693.0
COPD	28	418	39.1	295.0

Vital Events	Reporting Period		
	March 2008	12 Months Ending with March 2008	
	Number	Number	Rates
Live Births	1,118	13,163	12.3*
Deaths	988	10,090	9.5*
Infant Deaths	(5)	(97)	7.4#
Neonatal Deaths	(5)	(74)	5.6#
Marriages	253	6,729	6.3*
Divorces	278	3,062	2.9*
Induced Terminations	398	4,978	378.2#
Spontaneous Fetal Deaths	45	851	64.7#
Under 20 weeks gestation	(40)	(774)	58.8#
20+ weeks gestation	(5)	(77)	5.8#

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,067,610

(c) Years of Potential Life Lost (YPLL)

Note: *Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.*

* Rates per 1,000 estimated population

\# Rates per 1,000 live births

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Ninety Years Ago, September 1918

C. Augustus Simpson, MD, in "Nodular Syphilis," described two patients, "each wrongly diagnosed with epithelioma." He cautioned: "A history of syphilis is seldom obtained, the patient purposely or carelessly forgetting the incidents."

In "Recent Progress in the Study of Certain Infections," Alex. M. Burgess, MD, advised: "As a result of the war the investigation of several of the infectious diseases has received a very strong stimulus. The need for more effective control of some of these, especially … pneumonia and epidemic meningitis, has become so urgent a matter that many of the best trained investigators in the fields of bacteriology and sanitation have been devoting their entire time to the subject."

In "State Hospital for Mental Diseases," Arthur H. Harrington, MD, noted that before 1870, "the insane chargeable to the State of Rhode Island and to various cities and towns…were cared for at Butler Hospital, in hospitals and asylums in other states, in various almshouses within the State, and in some cases patients were entrusted to the care of persons who would agree to provide for them at the lowest price." After 1879, the state linked the care of the "insane" "to that of the poor, reformatory, and correctional classes." "Even today the line of cleavage between the mentally sick with other classes is somewhat obscured because the unfortunates afflicted with mental disease, the maimed in body, minor offenders against the law as well as criminals of all grades…are all located at Howard." In 1918 the capacity of the hospital "without crowding" was 1385 patients, costing $900,000.

Fifty Years Ago, September 1958

Congressman John E. Fogarty contributed "Medical Research in the Prevention and Treatment of Tuberculosis" [an address given before the National Tuberculosis Association Convention, Philadelphia].

In "New Regulations Imposed for Civilian Medicare Program," the Department of Defense listed new rules, following Congressional action on Medicare appropriations.

An Editorial, "The National Foundation," discussed the transition of the National Foundation for Infantile Paralysis [devoted to polio research] to the National Foundation.

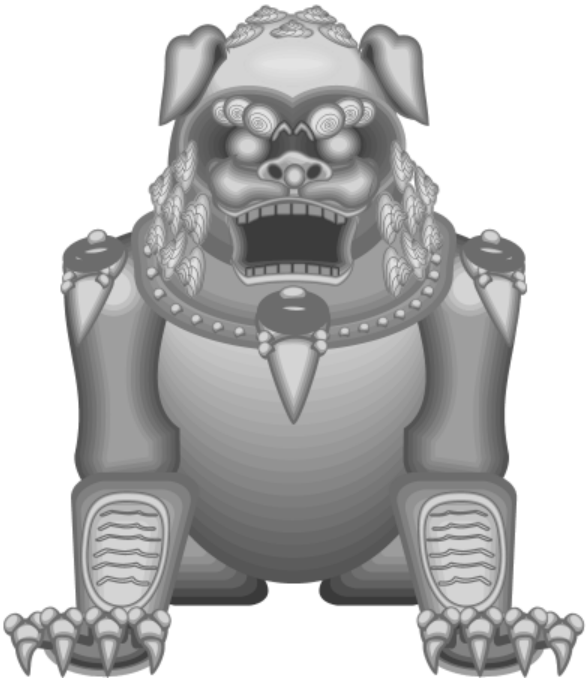
Twenty-Five Years Ago, September 1983

An Editorial, "The Specter of Alzheimer's Disease," by Stanley M. Aronson, MD, cited statistics: 1% for people ages 65-74, 4% for ages 75-84, 10% for ages 85 and older.

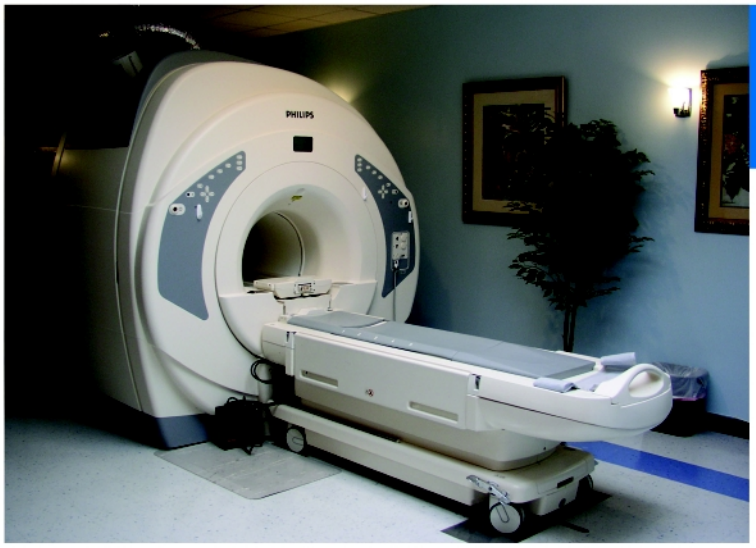
Ralph Barlow, pastor, Beneficent Congregational Church, Providence, in "Senile Dementia: Metaphor for Our Time," explained that his father had "sunk" into senile dementia over 10 years. The condition was successively diagnosed as "arteriosclerosis, organic brain syndrome, and finally, Alzheimer's Disease." He spent his last 3years in a nursing home, where his relationships with others deteriorated, echoing many relationships in American society.

James R. McCartney, MD, and Linda Palmateer, RN, MS, in "Dementia and Delirium: Detection in the General Hospital," urged clinicians to give a "high priority" to the detection and management of dementia and delirium.

A. Hunter Dupree, PhD, George Littlefield Professor of History Emeritus, Brown, had cared for a demented relative for 20 years. Professor Dupree contributed "A Strategy for Those in the Shadow of Alzheimer's Disease," He urged "Government and the health professions [to] support efforts to solve the biological, social and human problems."



The Name of Choice in MRI



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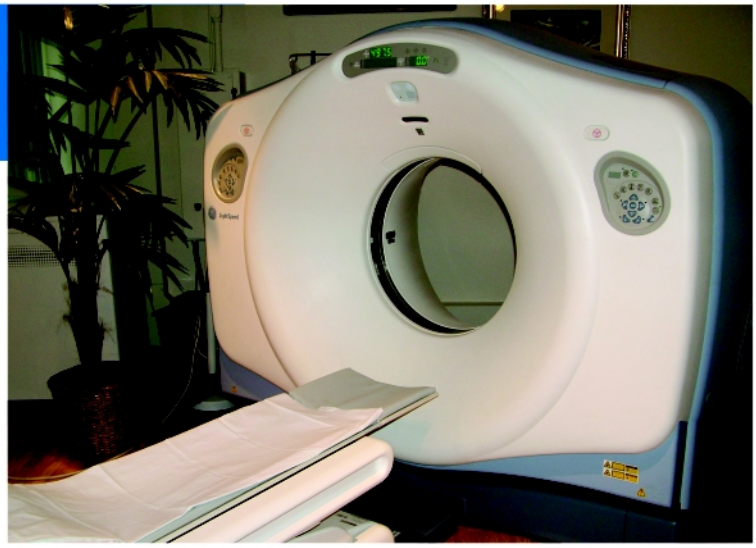

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