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Summary Report of the Meeting:

Methadone Mortality – A Reassessment

Sponsored by the
Center for Substance Abuse Treatment
Substance Abuse and Mental Health Services Administration

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Dear Colleague:

This report summarizes the presentations and discussions at the July 20, 2007 meeting, "Methadone Mortality – A Reassessment," which was sponsored by the Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration (SAMHSA). The meeting brought together epidemiologists, clinicians and educators, regulatory and enforcement officials, patient advocates, and policymakers for an in-depth reassessment of the current knowledge base on methadone-associated deaths and a review of progress in addressing the situation.

Methadone has a long, successful history as a potent analgesic and a highly effective medication for reducing the morbidity and mortality associated with opioid addiction. However, diversion, abuse, and deaths associated with many opioid medications, including methadone, have become a significant public health concern.

As the Federal agency tasked with oversight of the Nation's opioid treatment programs, SAMHSA is concerned about these developments. Accordingly, in May 2003, SAMHSA convened a meeting entitled "National Assessment of Methadone-Associated Mortality." Participants were tasked with reviewing the available data on methadone-associated deaths; determining whether and to what extent the reported increase in such deaths might be related to the clinical practices of SAMHSA-monitored OTPs; and formulating recommendations to address the problem.

At our July 20th meeting, SAMHSA convened a group of experts to reassess the situation, review the progress made to date, and provide advice and guidance on needed modifications or additions to the strategies currently being pursued. This document summarizes the information presented and conclusions reached, as well as strategies and action plans endorsed by the participants.

Those of us at SAMHSA found this to be a very valuable session, and trust that this report captures both the content and the collaborative spirit that marked the session.

Sincerely,

H. Westley Clark, M.D., J.D., M.P.H., CAS, FASAM

Director
Center for Substance Abuse Treatment

BACKGROUND AND OVERVIEW OF THE PROBLEM

Methadone is an important medication for the treatment of opioid use disorders and for chronic pain. It is a well-studied, safe, and powerful medication when prescribed and consumed properly. Methadone has been used for more than 40 years in the treatment of drug addiction, and its use for the treatment of pain has increased in the last 5 to 10 years.

Methadone is life saving, yet it presents special challenges. Some pharmacologic and pharmacokinetic properties of methadone can lead to harm if it is misused or used for nonmedical purposes. The short duration of analgesic effect with methadone and significantly longer elimination half-life increase the risk for methadone toxicity (FDA Web site). Methadone can cause fatalities among individuals who have not developed any tolerance to opiates. Deaths have occurred among children and adults who have accidentally taken methadone. Fatal intoxications have also been observed during the first weeks of treatment and adjustment of the methadone dose.

The lack of a common nomenclature and uniform case definition that distinguish between deaths caused by methadone and deaths in which methadone is a contributing factor or merely present make it difficult to determine the true number and nature of methadone-involved deaths nationwide. Despite this caveat, it is clear that methadone-associated deaths have continued to rise since the 2003 National Assessment meeting. At the same time that methadone's role in overdose deaths is real and substantial, deaths also have been escalating for other opioids such as oxycodone and hydrocodone.

According to FDA data, sales of methadone have increased as have the number of prescription; however, the causes of methadone-associated deaths remain unclear. Some data suggest that the deaths are most likely the result of the accidental misuse of the drug rather than intentional abuse. Several risk factors for methadone-related mortality have been identified: (1) the concomitant use of benzodiazepines, other opioids, and/or alcohol; (2) an elevated risk of some patients for Torsades de Pointes; (3) inadequate or erroneous induction dosing and monitoring by physicians, primarily when prescribing methadone for pain; and (4) drug poisoning that occurs as a result of diversion of the drug and its nonmedical use.

In 2006, Paulozzi, Budnitz, and Zi hypothesized that the large increases in deaths involving methadone (and other opioid analgesics) are related to increases in the prescriptions for opioid analgesics, as physicians increasingly prescribed it for chronic pain. The researchers reported that the increase in deaths tracked the increase in methadone used as an analgesic rather than its use in OTPs. Without reporting by OTPs of overdose events and deaths of patients, however, some key questions about methadone deaths will remain unanswered.

The increased scrutiny of methadone use in light of the rise in fatalities underscores the importance of exploring the extent of the problem, the benefits of the medication, the risks associated with its use, and the need to identify and take timely and effective action to reduce harm to those who use it for addiction treatment and in managing chronic pain.

PURPOSE OF THE REASSESSMENT

SAMHSA's role in monitoring adverse events related to methadone is embedded in both its statutory authority and the agency's commitment to promoting the public health. In 2001, the Secretary of Health and Human Services delegated to SAMHSA the responsibility for regulation and oversight of the Nation's opioid treatment programs (OTPs).

SAMHSA's current actions to address methadone-associated deaths began in 2002, spurred by reports of drug diversion, abuse, and deaths involving many opioid medications, including methadone. SAMHSA already was collaborating with the CDC, DEA, NIDA, and FDA, as well as with agencies in some of the States most directly affected by rising methadone mortality rates. Their reports, coupled with an increase in requests for consultation and assistance from State authorities and practitioners in the field, created added urgency for SAMHSA to evaluate and address the causes of the increase.

To assist it in developing a comprehensive plan and priorities, SAMHSA convened a multidisciplinary group of more than 60 experts – including representatives from various Federal and State agencies, researchers, epidemiologists, pathologists, toxicologists, medical examiners, coroners, pain management specialists, addiction medicine experts, and others – to re-evaluate and update the findings of the 2003 National Assessment. Participants were tasked with:

- Reviewing current data on methadone-associated deaths.
- Determining whether and to what extent such deaths might be related to the clinical practices of SAMHSA-monitored OTPs.
- Formulating strategies and action steps to address the problem.

The information presented, discussions, and conclusions of this distinguished group are summarized here.

FINDINGS OF THE REASSESSMENT

Participants at the 2007 Reassessment of Methadone-Associated Mortality reported six overall findings:

- Methadone-associated deaths continue to rise as supported by medical examiner, toxicology, and other data sources.
- Males 35 and older had the highest rate of methadone-associated deaths, approximately twice that of females.
- The reason for the majority of methadone-associated deaths is often unknown, but if known, is largely the result of accidental exposures.
- All forms of methadone distribution continue to rise, with the greatest increases in distribution for the tablet form and going to pharmacies.
- Prescriptions for methadone have risen, although they are far lower than for other opioids.
- Circumstances of methadone-associated deaths vary by State, suggesting a complex phenomenon.

An Update on Activities to Address Methadone-Associated Deaths

The following table provides a brief overview of activities that are representative of those that have been undertaken to address the rising number of methadone-associated deaths. They are presented in the following categories:

- Uniform nomenclature, case definitions, and standards for toxicological testing
- Data acquisition and analysis
- Training of health care professionals
- Public information
- Public policies

Uniform Nomenclature, Case Definitions, and Standards *Uniform nomenclature, case definitions, and standards for toxicological testing need to be in place regarding methadone to encourage uniform reporting by medical examiners and coroners and to support analysis.*
American Pain Society, American Academy of Pain Medicine, and American Society of Addiction Medicine ▪ Jointly developed a model nomenclature widely disseminated in journals and on Web sites. (see Appendix C)
Mallinckrodt (now Covidien) ▪ Considering a proposal to fund research to clarify issues surrounding deaths attributed to methadone involving medical examiners, physicians, epidemiologists by reviewing methadone-attributed mortality in Utah.
National Association of Alcohol and Drug Abuse Directors ▪ Surveyed State Methadone Authorities (SMAs) on whether medical examiners distinguished between deaths caused by methadone and deaths in which methadone is a contributing factor or is merely present. Many States reported any presence of methadone was considered a methadone overdose death, even if toxicology reports showed toxic levels of other drugs. Survey results are available in a NASADAD March 2007 *Issue Brief*. (see Appendix C)
Substance Abuse and Mental Health Services Administration ▪ The Working Group on Case Definitions drafted a statement of model uniform case definitions. Following peer review and validation, it will be submitted to NAME for adoption. (see Appendix C) SAMHSA will assist in disseminating the new definitions to medical examiners and coroners nationwide.

Data Acquisition and Analysis *Greater flexibility is needed in the design and evaluation of datasets and the performance of data analyses. Procedures for accessing new and existing data also should be simplified.*
American Association for the Treatment of Opioid Dependence ▪ Gathers anecdotal reports from members on changing patterns of opioid use and abuse being reported by newly admitted patients. As a result of these reports, a study was launched in January 2005 in 75 OTPs and 30 States to track changing characteristics of patients. The study is part of the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system. (see *Drug and Alcohol Dependence*, 2007)
Drug Enforcement Administration ▪ Maintains three data systems with information about methadone and other controlled substances: (1) ARCOS-Automation of Reports and Consolidated Orders System-summarizes reports from manufacturers and distributors regarding their controlled substances transactions from manufacture, importation, to distribution; (2) NFLIS-National Forensics Laboratory Information System-collects results of drug analyses conducted by forensic laboratories; and (3) STRIDE-System to Retrieve Information from Drug Evidence-contains information on drug evidence seized by the DEA.
Food and Drug Administration ▪ Maintains the MedWatch Adverse Event Report System (AERS) that allows (does not require) physicians to report patients' adverse reactions to prescribed drugs.
Mallinckrodt (now Covidien) ▪ Obtained longitudinal patient, prescription, and outcomes data on methadone. ▪ Subscribed to a national pharmacy benefits management database to obtain data on methadone use. ▪ Obtained data from the FDA AERS system for analysis.
National Association of State Alcohol and Drug Abuse Directors ▪ Surveyed SMAs on methadone-associated deaths, including increases, newspaper articles about such deaths, steps taken by OTPs to reduce such deaths, efforts to better define such deaths, and other initiatives. There were 22 respondents (see Appendix C).
National Institute on Drug Abuse ▪ Convened a panel session on methadone-associated mortality during the June 2003 Community Epidemiology Work Group meeting.
RADARS ▪ Obtains quantitative and qualitative information on the relative rates of abuse, addiction, and diversion of commonly prescribed analgesics. The dataset is not available to the public and is operated by the Rocky Mountain Poison Control & Drug Center.

Substance Abuse and Mental Health Services Administration

- Maintains data collection activities that include: (1) DAWN-the Drug Abuse Warning Network-collects data on drug-related deaths from medical examiner and coroner systems in about 50 metropolitan areas and 8 States with centralized medical examiner systems. State-level rates of death can be calculated. Mortality data can be analyzed based on manner of death, drugs involved, and decedent demographic characteristics, among other elements. The Emergency Department component of DAWN collects data on morbidity associated with drug use, misuse, and abuse. National estimates and estimates for some metropolitan areas are produced annually. (2) NSDUH-the National Survey on Drug Use and Health-collects data on nonmedical use of methadone in a respondent's lifetime. (3) TEDS and N-SSATS-the Treatment Episode Data Set collects data on admissions to addiction treatment programs (primarily publicly funded) and includes information on planned use of opioid therapy in treatment. The National Survey of Substance Abuse Treatment Services surveys all known substance abuse treatment facilities and collects data on whether facilities offer methadone and buprenorphine treatment services and the number of clients that receive these services.
- Commissioned independent studies of methadone-associated morbidity and mortality from public sources such as State Medicaid drug utilization reviews and private sources such as IMS Health that track prescriptions.
- Tracks and reports published studies of methadone-associated morbidity and mortality. (see Appendix C)

Veterans Administration

- The Pharmacy Benefits Management Strategic Healthcare Group (PBMSHG) is evaluating methadone-associated deaths and other adverse events relative to those of other opioids through (1) analysis of all-cause mortality and respiratory depression among patients prescribed methadone versus other opioids; (2) a new VA-wide Adverse Drug Experience Reporting System; (3) the VA National Center for Patient Safety database of voluntary reports of adverse events and near misses considered for Root Cause Analyses; and (4) the VA MedWatch database that relays adverse drug reactions to the FDA's MedWatch program.

Training Health Care Professionals in the Management of Pain and Addiction

Health care professionals need better training in how to manage pain and addiction, both of which are medical disorders for which health professionals have an ethical obligation to provide the best available treatment.

American Association for the Treatment of Opioid Dependence

- Adopted a policy statement in March 2004 that recommends every OTP ensure their medical practitioners are specially trained and subscribe to current therapeutic practices regarding use of methadone and buprenorphine.
- Produces and offers, in collaboration with NIDA, a 1-day training on opioid maintenance pharmacotherapy for clinicians during each annual conference.
- Offers risk management training events during national conferences in collaboration with the Legal Action Center, CSAT/SAMHSA, treatment practitioners, and representatives of the insurance industry.

American Medical Association ▪ Supports online pain education course on its Web site, a statement of AMA policy on the use of controlled drugs to control pain, and links to other educational resources. (see Appendix C)
Federation of State Medical Boards ▪ Promulgated "Model Guidelines for the Use of Controlled Substances for the Treatment of Pain" (updated in 2004) that have been adopted by 20 States and endorsed by the DEA, APS, National Association of State Controlled Substance Authorities (NASCSA), and many others. (see Appendix C)
Food and Drug Administration ▪ Conducted a conference call with health care provider groups in November 2006 to draw their attention to the new label warnings for methadone.
Mallickrodt (now Covidien) ▪ Strengthened programs to educate health care professionals, patients, and the public through the Addiction Treatment Forum and an associated Web site at ATForum.com. The ATF focuses on the safe and effective prescribing and use of methadone for opioid addiction. It offers a quarterly evidence-based newsletter, a series of peer-reviewed clinical guidance reports for practitioners on topics regarding the effective and safe prescribing of methadone (see Appendix C). ▪ Developed the Mallinckrodt Methadone Training Program, with eight modules, for OTPs. ▪ Developed Pain Treatment Topics and launched a Web site providing clinical news, information, and research for a better understanding of evidence-based pain management practices. An important emphasis on the Web site is the safe and effective prescribing and use of opioid analgesics. (see Web site www.Pain-Topics.org)
National Institute on Drug Abuse ▪ Co-sponsored a meeting with the AMA in March 2007 on "Pain, Opioids, and Addiction: An urgent Problem for Doctors and Patients" to inform researchers and practitioners about the science surrounding addiction and pain management.
New York-New Jersey AIDS Education and Training Center ▪ Published "Pain Management/Addiction Management Medications and HIV Antiretrovirals-A Guide to Interactions for Clinicians" in 2004. The booklet reviews data on potential interactions between antiretroviral medications and a variety of drugs (including methadone) used to treat pain and addiction. (see Web site www.nynjaetc.org)
Substance Abuse and Mental Health Services Administration ▪ Published a Treatment Improvement Protocol (TIP) on management of addicted patients who have co-occurring psychiatric disorders. ▪ Published a *Substance Abuse in Brief Fact Sheet* (Vol. 4, Issue 1) on "Pain Management without Psychological Dependence: A Guide for Healthcare Providers." ▪ Sponsored workshops at annual meetings of the American Association for the Treatment of Opioid Dependence. ▪ Developed patient intake questionnaire (PODS) to provide physicians with immediate printout of a patient's drug use history and other risk factors for problems with opioid analgesics.

Computer software is under development.

- Participated with the American Academy of Pain Medicine, American Academy of Family Practitioners, and other medical organizations to develop a CME course on the use of methadone to treat pain. Pilot sessions were completed and initial course offerings are scheduled for September 2007, with a possible offering on Medscape. (see Appendix C)
- Offered symposium on the use of methadone to treat pain at the 7th International Conference on Pain and Chemical Dependency in June 2007.

Veterans Administration

- Collaborated with the Department of Defense (DoD) to develop a clinical practice guideline on opioid therapy for chronic pain.
- Offered presentations on pain management at the VA/DoD conference on Evolving Paradigms: Providing Health Care to Transitioning Combat Veterans.
- Planning to add a new chapter on methadone dosing to an existing Web-based continuing education program on use of opioids in acute and chronic pain.
- Planning to co-lead a breakout session on methods to promote education on the appropriate use of methadone at a VA Clinical Pharmacy Programming Conference in September 2007.
- Planning to highlight methadone as part of the VA's High Alert Medications-Opioids initiative.

Public Information

Professional organizations and regulatory agencies need to present scientific evidence and credible data to counter misinformation about methadone and "methadone clinics" (OTPs) presented in the mass media. Professional associations, provider organizations, and advocacy groups need to be engaged in public information activities. The public also needs to know that methadone-associated mortality is being addressed and that when methadone is prescribed, dispensed, and used appropriately, related mortality is virtually eliminated.

American Association for the Treatment of Opioid Dependence

- Developed positive media messages regarding methadone treatment and developed the first community education kit "Medication Assisted Treatment for the 21st Century."
- Developed training materials for treatment professionals and patient advocates to develop clear messages for the media about the opioid treatment system, including media training events at the AATOD annual conferences.
- Convened a specialized media training strategy session in August 2007 on methadone-associated mortality.

Food and Drug Administration

- Developed patient package inserts for methadone products regarding the risk of methadone use. (see Appendix C)

Mallinckrodt (now Covidien)

- Addiction Treatment Forum produced a series of 21 patient brochures available to Mallinckrodt clinics and for download at no cost. (see the Website www.ATForum.com)

Substance Abuse and Mental Health Services Administration

- Developed an advertising campaign to alert the public about potential misuse of prescription medications, including take-home doses of methadone prescribed for addiction or pain. (see Appendix C)

Veterans Administration

- Posted Methadone Dosing Recommendations for Treatment of Chronic Pain on its Web site, suggesting that methadone can be safely used when initial doses are small, conversion ratios are adjusted to the previous opioid dose, and dosage is slowly titrated to patient response. (see the Website: www.pbm.va.gov/monitoring/Methadone)

Public Policies

Policies regarding the use of opioid medications should address the needs of law enforcement and regulatory agencies, professional education, pain management, and addiction treatment providers.

Drug Enforcement Administration

- Regulates methadone, a Schedule II substance of the Federal Controlled Substance Act, and sets the annual production quota for methadone. Reports that the quota increased by 250 percent between 1998 and 2006, with increased use primarily associated with use of methadone in pain management rather than addiction treatment.

Food and Drug Administration

- Updated labels for methadone products to provide current information on pharmacology, drug-drug interactions, and dosing recommendations. New warnings (boxed) alert practitioners to the risk of accidental overdose during treatment initiation and during conversion from other opioids, risk of fatal respiratory depression, and risk of cardiac conduction effects including QT prolongation and Torsades de Pointes. (see Appendix C)

State Prescription Monitoring Programs

- Prescription monitoring programs (PMPs) facilitate the collection, analysis, and reporting of information on the prescribing, dispensing, and use of controlled substances. Most such programs employ electronic data transfer systems, under which prescription information is transmitted from the dispensing pharmacy to a State agency, which collates and analyzes the information. Monitoring programs that required the use of special prescription forms (once known as "triplicate prescription programs" or "multiple-copy prescription programs") have largely been phased out, although the California, New York, and Texas PMPs employ special state-issued prescription forms in combination with electronic reporting (Alliance for Model State Drug Laws, 2006), and the Washington State's medical board requires some physicians to use them for a defined period of time as part of a practice monitoring program.

Discussion and Action Planning

Meeting participants met in six small groups to discuss specific areas of interest and concern related to methadone mortality. These groups identified and discussed a wide range of issues and evidence pertinent to these issues, and developed strategies and possible action steps for CSAT/SAMHSA as well as others. These small group discussions are summarized below.

Group 1: Improving Case Definition and Classification

Co-Chairs: Bruce Goldberger, Ph.D., DABFT and Marcella Sorg, Ph.D., DABFT

Key Discussion Issues

Lack of common nomenclature and toxicological standards. CSAT's draft statement on uniform case definitions for classifying deaths induced by or related to the use of prescription opioids was a good first step. However, professional organizations such as the National Association of Medical Examiners (NAME), Society of Forensic Toxicologists (SOFT), and the American Academy of Forensic Sciences (AAFS) need to agree on a uniform nomenclature that clearly distinguishes physiologic dependence and drug tolerance (which occur with many commonly used opioid medications) from addiction (which is a chronic, relapsing, neurobiological disorder with behavioral manifestations). Standards also should be developed to guide toxicological testing in cases of suspected drug-induced deaths. Such a process would be more likely to achieve results that are eventually adopted by medical examiners and coroners. Further, without common nomenclature, the comparison of data from various epidemiologic databases or studies of methadone-associated mortality is made unduly difficult. Most medical examiners and coroners favor common nomenclature and toxicological standards, but this is a State function and thus not susceptible to intervention at the national level.

Variations in cause of death reporting. Cause of death continues to be classified and reported differently from one jurisdiction to the next. In some cases, methadone is reported as a cause of death when it is only a contributory factor or not a factor at all, while in other cases it is the cause of death but is not reported as such. Scientifically concise, universally accepted toxicological standards and classification systems could address the critical distinction between deaths caused by methadone and deaths in which methadone is a contributing factor or merely present. If such standards are adopted, investigative techniques for medical examiners and coroners can be enhanced and standardized.

Tracking and reporting drug-related deaths. The development of a central repository for reporting opioid-related deaths would facilitate data compilations and analyses. To meet this urgent need, a new National Drug Mortality Reporting System (NDMRS) could be created. Such a system would involve NIDA, National Forensic Laboratory Information System (NFLIS), Office of Applied Studies at SAMHSA, SOFT, NAME, and the CDC. Representatives of NDMRS' participating agencies would meet regularly to share data, identify emerging problems, and develop prevention strategies.

Digital platforms also can be useful in enhancing reporting. For example, the adoption of electronic medical records may be helpful in developing a template that captures the needed data

elements. If case data are entered online, case definitions can be embedded into the software and employed in a standardized manner. NAME is exploring this type of approach.

The larger issue of increased drug-poisoning deaths. The dramatic increase in drug poisonings reported by NCHS was of particular interest and concern. Methadone deaths need to be viewed as part of a larger problem of increasing drug poisonings. A strong, coordinated Federal response to this larger problem is needed, which may involve an early warning system. CSAT/SAMHSA could play a key part in this response.

Group 2: Improving Data Collection and Analysis

Co-Chairs: Jane C. Maxwell, Ph.D., and Nina Shah, Ph.D.

Key Discussion Issues

Complexities in understanding methadone deaths. Data show that deaths from methadone continue to trend upward and are actually increasing at a greater rate than deaths from other opioids. Nonetheless, obtaining an accurate picture of methadone deaths is complex, in part because medical examiners and coroners differ in their determination of cause of death. It is hard to assess mortality data if the definition of a methadone death is not relatively consistent across the country. Distinctions among methadone data such as cause of death, related to death, or associated with death are often lost. In addition, more discriminative data are needed, such as age of decedent and geographic region, to begin to understand the phenomenon.

Methadone as cause of death. Methadone deaths are not a singular phenomenon and are more complex than was perceived in 2003. These deaths have not been linked specifically to OTPs; at the same time, they have not been linked exclusively to treatment for pain. This actually may be a false dichotomy, since a growing number of patients taking prescription opioids for pain become addicted to them. Patients being treated for pain may suffer from depression and are often cognitively impaired, making it difficult to keep track of the methadone taken. The unintentional taking of too much prescription methadone falls under misuse rather than abuse, as when individuals are trying to get high. Diversion of methadone is an additional, serious problem. A more effective approach might be to focus on the site of treatment, drawing distinctions between office-based treatment and OTPs, rather than on the use of methadone to treat addiction versus pain.

Circumstances surrounding methadone deaths. The circumstances surrounding methadone deaths have been oversimplified, such as those presented in the 2003 scenarios. OTP staff and patients, for instance, need to appreciate how powerful methadone is and that proper dosing is critical. It was pointed out that even small doses of diverted methadone can result in death.

Data on opioid-related deaths. An understanding of methadone deaths requires an ability to examine data on all deaths related to opioid analgesics. A related concern is the need to provide OTP data to Prescription Management Programs (PMPs) since many patients do not tell their physicians they are taking methadone. As suggested in 2003, a nationwide reporting system for opioid or all-narcotic deaths is still desirable. Alternatives to this option include recruiting physicians in key geographic areas into a surveillance system, similar to DAWN, for which they report data on sentinel events (e.g., deaths related to methadone); adding new drugs to existing databases such as DAWN when they become public health threats; and adapting the CDC's system for real-time reporting of methadone deaths.

Group 3: Reducing Methadone Deaths Associated with Addiction Treatment
Co-Chairs: Mark Parrino, M.P.A. and Joan Zweben, Ph.D.

Key Discussion Issues

OTPs and methadone deaths. OTPs are subject to more scrutiny than most other types of substance abuse treatment programs, and when methadone-associated deaths occur, OTPs are examined. Yet non-OTP treatment providers now prescribe more methadone than OTPs. One reason for this attention to OTPs is a lack of sound and accurate data about methadone deaths. There is uncertainty about how many methadone deaths are attributable to OTP treatment, misuse of take-home methadone, methadone diversion, and other causes. Without sound data, it is not yet possible to determine if methadone-associated deaths cluster around certain factors or occur randomly. Data on all OTP deaths and near-death incidents among OTP patients would provide useful information although programs will vary widely in their ability to provide these data.

Risk factors for methadone mortality and OTPs**.** Take-home medications, induction, and screening activities may play a role in methadone-associated mortality. Allowing take-home methadone privileges is often perceived as increasing the risk for related mortality, although research data do not support this idea. OTPs try to balance the desire to keep patients safe and help them normalize their lives. The take-home and onsite dosing policy of an OTP needs to be determined by and proportionate to the scope of the problem in the specific region and the treatment population (e.g., too many take-home related methadone deaths occur in children). At the same time, research data indicate that the induction phase of treatment represents the greater mortality risk for OTP patients. Adhering to standardized induction protocols has not been shown to play a role in methadone-associated deaths, although anecdotal evidence suggests otherwise. During induction, clinicians may monitor individuals for adverse reactions to methadone for only a few hours, while observation for longer periods may be needed. Some patients need more than outpatient care as well. Residential treatment programs are best able to provide 24-hour supervision, but many of these programs do not accept methadone patients. Standardized screening practices, such as routine screening for other substances of abuse, are also important to pinpoint variations in program practices that may play a role in methadone-associated deaths.

Patient and program education. Aggressive educational efforts regarding methadone are needed for patients and program staff. Patients will be less likely to use methadone in a risky manner and program staff will be more likely to provide effective counseling if they fully understand the risks associated with methadone. Patient education should engage the patient in the planning and delivery of information; include a Web site with pamphlets and educational resources assembled through CSAT that are concrete, simple, and repetitive; and educate family members. It is especially important to find ways to communicate with patients during the induction stage since this is when the greatest number of OTP methadone-associated deaths occurs.

Group 4: Reducing Methadone Deaths Associated with Pain Treatment

Co-Chairs: Margaret M. Kotz, D.O. and Howard A. Heit, M.D., FACP, FASAM

Key Discussion Issues

Data and analysis pertaining to methadone-associated deaths and treatment for pain. A clearer and more nuanced definition of methadone-associated death is needed to support data analysis. With few or unclear criteria for assigning a causal relationship between methadone and a death, the ability to draw reliable conclusions about methadone is undermined. While more information on methadone-associated deaths is now available than in 2003, data such as those from FDA could be usefully analyzed to determine demographic characteristics, length of time methadone had been prescribed, and when death occurred. Further, the American Academy of Family Physicians has called for Federal support of longitudinal studies on the effectiveness of methadone, and all opioids, in the treatment of chronic pain.

Guidelines for prescribing an opioid. The standard of care for the initial screening of patients who are prescribed an opioid should include questions about past and current use of alcohol, tobacco, and other drugs. Most medical education courses do not address this type of screening before deciding whether to prescribe opioids or other controlled drugs for pain. A challenge to this standard of care is that physician reimbursement for time spent screening and educating patients, and monitoring and recording patient activities is not as great as for performing procedures. Third-party payers must begin reimbursing physicians for the time to initiate and manage long-term treatment of chronic pain with opioid medications. The American Pain Society is preparing evidence-based guidelines for the use of opioids to treat pain that could support and encourage such reimbursements.

Professional education requirements. Medical professionals require knowledge of the proper procedures for prescribing controlled drugs as demonstrated by successfully completing a CME course or by passing an examination before a physician receives a DEA number. Medical specialty boards might include a test for prescribing opioids in their certification and recertification processes. A high priority needs to be placed on making available CME courses on the use of methadone for pain and for prescribing methadone that comply with ACCME standards.

Group 5: Medical Complications Associated with Methadone Use

Co-Chairs: Stephen Cantrill, M.D., FACEP, and Mori J. Krantz, M.D.

Key Discussion Issues

Risk for Torsades de Pointes (cardiac arrhythmia) among methadone users. A significant portion of deaths among methadone users cannot be avoided so efforts should focus on reducing avoidable complications of methadone use. Data from a number of studies suggest that a medical complication of methadone use is an increased risk for cardiac arrhythmia. While more research is needed, research shows that methadone is among the top five causes of cardiac arrhythmia.

One study compared buprenorphine, methadone, and LAAM and found that patients taking between 60 and 100 mg of methadone for more than 16 weeks had more than a 10 percent chance of reaching the threshold at which the risk for cardiac arrhythmia increases. Nonetheless, a national survey of certified OTPs found that fewer than 25 percent of medical directors were

aware that methadone could lead to cardiac arrhythmia. Physicians need additional medical education and regulatory steps were suggested as well to induce clinicians to take action.

Improving patient safety. While some treatment programs require all patients to have an ECG (the only currently available method to assess the risk of sudden cardiac death) before they are prescribed methadone, there is little evidence to suggest that universal screening would be effective in preventing sudden cardiac death and it could increase the cost of treatment. SAMHSA has already proposed ECG screening, but it has been rejected as too costly. Several options were discussed to ensure clinicians consider the cardiac risks associated with methadone use, including national guidelines for methadone treatment programs that could serve as a model for other treatment settings and clinician education; guidelines that are tied to institutional accreditation, a methadone-specific certification of competency, and a national task force to recommend safety improvements for methadone use. These options raised issues of decreased access to methadone, increased costs, and physician willingness to undergo certification. For patients found to be at high risk for a cardiac event, buprenorphine should be an option, methadone doses can be decreased or split, or MSContin can be prescribed.

Group 6: The Role of Regulatory and Law Enforcement Agencies

Co-Chairs: William L. Harp, M.D., and Charles Cichon

Key Discussion Issues

Improving data on methadone-associated deaths. Many medical examiners and coroners lack training and common definitions that will provide accurate, consistent data regarding methadone deaths. CSAT is working to draft model uniform case definitions for review and possible endorsement by NAME. Although available data indicate methadone-associated deaths have continued on an upward trend since 2003, these data may be incomplete.

Improving methadone prescribing. Some physicians do not know how to prescribe methadone and an enhanced collaboration between government regulators and medical and other groups is needed. This collaboration could include the launch of the CME course being developed by CSAT on the use of methadone to treat chronic pain (set for September 2007); prescribing courses offered by Boards of Medicine, and outreach to medical students and physicians in the VA health care system. Patient information also needs to be improved to be clearer, easier to read, and easier to understand.

KEY STRATEGIES AND ACTION STEPS

This section consolidates the discussions within the six small groups and the related strategies and action steps that were the products of those groups. Participants in the six groups assessed the updated methadone data and, in light of the findings, identified relevant strategies and future action steps for CSAT/SAMHSA and other organizations. As reflected here, in numerous instances the individual group deliberations resulted in common findings and similar strategies and action steps, suggesting further consensus regarding their significance.

Data, Case Definition, Nomenclature, and Uniform Standards for Classifying Methadone-Associated Deaths

The rate of methadone-associated deaths has continued to increase despite steps taken since the 2003 National Assessment. Worse, the available data may be incomplete: for example, they may not include some deaths associated with QT prolongation and other cardiac or respiratory complications. More data are available today than in 2003, yet there still is a need for more nuanced, detailed analysis. For example, FDA data could be analyzed to determine demographic characteristics, length of time methadone had been prescribed, and whether the death occurred during induction or at another point in treatment.

Criteria for assigning a causal relationship between methadone and a death are not clearly defined, which undermines the ability to draw reliable conclusions. Cause of death continues to be reported differently from one jurisdiction to the next. In some cases, methadone is reported as a cause of death when it is only a contributory factor or not a factor at all, while in other cases it is the cause of death but is not reported as such. Most Medical Examiners and Coroners favor standardization of nomenclature and case definitions, but this is a State function and thus not susceptible to intervention at the national level.

Because of the problems cited above, there are not sufficient data to support the hypothesis that methadone deaths are rising in parallel with deaths from all opioid analgesics. Available data do support the hypothesis that the increase in methadone deaths is not linked to addiction treatment, but do not support the theory that the increase is linked exclusively to the treatment of pain. Clearly, the situation is more complex than at the time of the initial National Assessment in 2003.

Strategies

Providing Context: CSAT/SAMHSA should develop a coordinated Federal response to the larger problem of drug-related poisoning, which may involve an early warning system. To achieve this goal, SAMHSA could convene a national meeting of stakeholders – including Federal and State agencies and health professions organizations – to address the overall epidemic of drug poisonings. SAMHSA also should communicate the findings of the July 20th meeting to the National Academy of Sciences, with a request for a comprehensive review. (Groups 1, 2, 5)

It also would be helpful to understand how data from various sources could be integrated to develop more comprehensive analyses. For example, it would be useful to compare data from IMS Health, ARCOS, or State prescription monitoring programs (PMPs) with medical examiner

data to assess methadone prescribing trends and patterns in regions that report increased cases of methadone-associated deaths.

Data Quality, Access and Analysis: In order to truly understand the data on methadone deaths, it is necessary to examine all deaths related to opioid analgesics. Ideally, each State would have at least one person dedicated to investigating all drug-related deaths. (Groups 1,2)

Comparison of data from various epidemiologic databases or studies of methadone-associated mortality is made unduly difficult by the fact that such databases do not employ a common nomenclature. Professional organizations need to agree on a uniform nomenclature that clearly distinguishes physiologic dependence and drug tolerance (which occur with many commonly used opioid medications) from addiction (which is a chronic, relapsing, neurobiological disorder with behavioral manifestations). Standards should be developed to guide toxicological testing in cases of suspected drug-induced deaths.

Procedures for accessing new and existing data should be simplified. Better information is needed on the uses and limitations of data from existing data sets and data collection systems.

Stronger relationships between public health officials and addiction professionals would facilitate reporting and tracking. For example, poison control centers often know about emerging problems before the CDC and the addiction community, but the channels to share such information are not readily available. Therefore, a centralized, national registry of drug-related deaths is urgently needed. The ability to quickly add emerging drug problems to data systems such as DAWN would be helpful. A good model is the CDC's system for real-time reporting of methadone deaths. SAMHSA should develop such a repository and allow multiple agencies at the national, State and local levels to share information. At the Federal level, such a system could involve the National Institute on Drug Abuse (NIDA), National Forensic Laboratory Information System (NFLIS), Office of Applied Studies at SAMHSA, SOFT, NAME, and the CDC. Representatives of participating agencies would meet regularly to share data, identify emerging problems, and develop prevention strategies. The Fentanyl Alert System is a useful model in this regard, because it connects police, public health, and other officials. State epidemiologists could take the lead. This could be part of a coordinated Federal response to the larger problem of drug-related poisonings. (Groups 1, 2, 4)

Data on Methadone as a Cause of Death: Cause of death (COD) continues to be classified and reported differently from one jurisdiction to the next. In some cases, methadone is reported as a cause of death when it is only a contributory factor or not a factor at all, while in other cases it is the cause of death but is not reported as such. Moreover, better information is needed to describe how methadone-associated deaths occur. For example, data could help us understand whether the drug's potential for lethality may be the result of a slow onset of action, leading to repeated dosing – and, ultimately, overdose – as an individual attempts to achieve the desired drug effect.

Scientifically concise, universally accepted toxicological standards and classification systems could address the critical distinction between deaths caused by methadone and deaths in which methadone is a contributing factor or merely present. Once such standards have been adopted, investigative techniques for medical examiners and coroners can be enhanced and standardized. (Groups 1, 4, 6)

A consensus process, led by SAMHSA/CSAT, could be used to begin to move toward standardized definitions. Such a process would be more likely to achieve results that are eventually adopted by Medical Examiners and Coroners. (Group 2)

In addition, many Medical Examiners and Coroners lack the training to differentiate between deaths where methadone is present and those where methadone is a causal or contributing factor.

For these reasons, most Medical Examiners and Coroners favor standardization of nomenclature and toxicological standards, but this is a State function and thus not readily susceptible to intervention at the national level. A consensus process is desirable and could be used to move more Medical Examiners and Coroners toward use of standardized definitions and classifications. Such a process would be more likely to achieve results that are acceptable to Medical Examiners and Coroners. (Groups 1, 6)

CSAT's draft statement on uniform case definitions is a good first step. To move the process forward, SAMHSA could contract with NAME, SOFT, and the American Academy of Forensic Sciences (AAFS) to conduct a consensus-building process and any necessary validation studies in support of the draft statement. In addition, accurate information is needed to identify the formulations and sources of methadone associated with fatalities (e.g., thefts, robberies or diversion from medical practices, pharmacies, or OTP clinics). For example, current data indicate that most methadone-associated deaths, where dosage form information is available, involve 5 and 10 mg tablets. However, it is not clear whether those tablets are obtained through legal prescriptions, prescription forgeries, other diversion tactics, or pharmacy thefts or robberies. (Groups 1, 2)

Digital platforms also can be useful. For example, the adoption of electronic medical records may be helpful in developing a template that captures the needed data elements. If case data are entered online, case definitions can be embedded into the software and employed in a standardized manner. The National Association of Medical Examiners (NAME) is exploring this approach.

Data on Methadone Users: More information is needed about the population being legitimately prescribed methadone for pain, including their health history, concomitant use of other medications, and current or past involvement with alcohol or other drugs.

Action Steps

FDA and/or NIDA should convene a national meeting of all stakeholders – including Federal and State agencies and health professions organizations – to address the larger epidemic of drug poisonings. The findings of that meeting should be provided to the National Academy of Sciences, with a request for a larger review. (Group 1)

CSAT/SAMHSA should:

1. Convene an expert panel to address the complexities in data collection and interpretation that have emerged since the initial National Assessment in 2003. (Group 2)

2. Take the lead in creating a new National Drug Mortality Reporting System (NDMRS). The new system would involve the National Institute on Drug Abuse (NIDA), National

Forensic Laboratory Information System (NFLIS), Office of Applied Studies at SAMHSA, SOFT, NAME, and the CDC. (Groups 1, 2)

3. Require OTPs to capture and report to NDMRS vital information about all patient deaths, including deaths of persons in treatment and those who have completed treatment but continue to be monitored. All causes of death should be reported, no matter how removed they may seem from treatment circumstances. Programs administrators and staff should be provided technical assistance on how to gather, analyze, and report death and near-death data. (OTPs vary widely in their ability to do this.) Many OTPs need guidance on how to use data to prevent a future event. Otherwise, the usefulness of the data will be lost. (Groups 2, 3)

4. Continue to work collaboratively with the group of experts who drafted the model uniform case definitions, and with NAME to seek their review and possible endorsement. (Groups 1, 6)

5. Require OTPs to report dispensing data to state Prescription Management Programs. (PMPs should make this information available to medical professionals, because too many patients don't tell their primary care physician that they are using methadone.) (Groups 2, 6)

Methadone in Addiction Treatment

Non-OTP treatment providers prescribe more methadone than do OTPs, yet OTPs are subjected to more political pressure and public and media scrutiny than most other types of medical treatment. This problem is compounded by the fact that the opioid treatment field does not know how many methadone-related deaths are attributable to methadone treatment, misuse of take-home methadone, methadone diversion, or other causes. Better data would give OTPs more leverage to respond when the efficacy and safety of methadone treatment are questioned.

Moreover, professionals in the addiction field may have gone too far in arguing that methadone is safe, without emphasizing "when used appropriately." It is clear that many health professionals, patients, and members of the public do not understand the dangers of using methadone in ways that do not conform to evidence-based guidelines.

Strategies

Professional Education: Health care professionals need better training in how to manage addiction, which is a medical disorder for which health professionals have an ethical obligation to provide the best available treatment. To do so, physicians and other health care professionals need credible, reliable information about the appropriate use of various therapies, including methadone. Such training should be part of the core educational curricula for all health care professionals who work in addiction treatment.

Medical staff of OTPs must be knowledgeable about methadone's pharmacokinetics and pharmacodynamics, as well as protocols for appropriate dosing and patient monitoring. Requiring certification of those who would prescribe methadone (as is done for those who would prescribe buprenorphine) is an option that may be more efficient at promoting practice change

than voluntary programs. However, issues of access, cost, and physician willingness to undergo certification should be considered before proceeding in this direction. All OTP staff are less likely to ignore the risks and more likely to provide effective counseling to patients when they fully understand the risks associated with misuse of methadone. (Groups 3, 5)

Some patients need more than outpatient care – they need 24-hour-a-day monitoring. Residential treatment programs are best able to provide this kind of supervision, but many will not accept methadone patients.

Data indicate that the greatest risk in the use of methadone occurs during the induction phase of treatment. There is a need to move beyond "cookie cutter induction" – a caution reinforced in CSAT's Treatment Improvement Protocol (TIP) 43. (Groups 3, 4)

Public Information: Better information is needed about the nature of education and prevention messages currently being communicated to and by the public, patients, practitioners, and the media. Patients are less likely to use or handle methadone in a risky manner when they are educated about the attendant risks. Given inaccurate or incomplete information, patients may be deterred from seeking treatment using methadone or other opioid drugs for legitimate medical problems, including both pain and addiction. (Groups 3, 6)

Take-home Medications: On the subject of take-home medications, OTPs experience tension between the desire to keep patients safe and to help them normalize their lives. Although allowing take-home methadone privileges may increase the risk of related mortality. Many programs give patients take-home doses of methadone to get them through the weekend, sometimes without considering patients' treatment and recovery history. (Group 3)

Research data do not support the idea that take-home medications increase the risk of methadone-related mortality. For those doing well in treatment, take-home medication is a reward for positive progress and a source of motivation to continue the recovery program. (Group 3)

Some jurisdictions require that OTPs operate 7 days a week so as to avoid the need for take-home doses, but that approach has serious drawbacks for programs and patients (program budgets must absorb the additional costs, program liability risks increase, and required attendance on weekends places an additional burden on patients. (Group 3)

Many deaths related to take-home methadone occur in children, because methadone take-home doses are in a liquid form that children may be tempted to drink. (Group 3)

Action Steps

Federal agencies should work with experts in addiction treatment to identify variations in OTP practices during patient screening to identify negative variations that may play a role in methadone-related deaths. (Group 3)

State Methadone Authorities should work with residential treatment programs to persuade them to accept patients who are taking methadone and other prescribed medications (such as psychiatric medications). (Group 3)

CSAT/SAMHA should:

1. Require physicians who are not credentialed in addiction medicine or addiction psychiatry to undergo special training if they become medical staff in OTPs (similar to the DATA 2000 requirements to prescribe buprenorphine).

2. Support aggressive training efforts for all OTP clinical staff.

3. Consult with experts/organizations in the field to develop criteria that allow individualized methadone dosing in addiction treatment to replace standard dosing protocols for induction.

4. Use the accreditation process to provide advice and technical assistance to OTPs on any procedures that may be weak. (Groups 3, 5, 6)

Methadone in Pain Treatment

All FDA-approved opioid medications, including methadone, are powerful and useful drugs in such treatment. On the other hand, inappropriate prescribing, misuse, and abuse of prescription opioids (including methadone) are serious public health problems attended by substantial morbidity and mortality.

At the time of the 2003 National Assessment, there was consensus that most methadone deaths were attributable to abuse of the drug. Today it appears that abuse accounts for only half of all methadone deaths. The other half are pain patients who are being mismanaged by physicians who lack sufficient knowledge or skills to use methadone in the treatment of pain. (Group 4)

Professional Education: Whenever a controlled drug is prescribed (especially an opioid), it should be the standard of care that the initial evaluation (screening) of the patient include questions about past and current use of alcohol, tobacco and other drugs. However, most medical education courses do not address the need to conduct this type of screening before deciding whether to prescribe an opioid or other controlled drug. (Group 4)

The fact that reimbursement is greater for procedures than for time spent in screening, diagnosis or monitoring works against the recommendation that physicians screen and educate patients, execute a written agreement about use of prescribed drugs, monitor patients regularly, and record those activities in the patient record. (Group 4)

Patient Information: It would be helpful to know what information individuals are receiving from their physicians when methadone is prescribed, and whether patients and prescribers fully understand the potential dangers of methadone misuse and abuse.

Better information is needed about the nature of education and prevention messages currently being communicated to and by the public, patients, practitioners, and the media. Given inaccurate or incomplete information, patients may be deterred from seeking treatment using methadone or other opioid drugs for legitimate medical problems, including both pain and addiction.

Strategies

Professional Education: Physicians need to understand methadone's pharmacology and "best practices" for its use, as well as specific indications and cautions to consider when deciding whether to use this medication. Accordingly, the diagnosis and treatment of pain, as well as the appropriate use of various therapies for its treatment, should be part of the core educational curricula for all health care professionals.

CSAT/SAMHSA was commended for its support of new medical education programs to meet this need.

Patient Information: The American Pain Society is preparing evidence-based based on an extensive review of the literature, for the use of opioids to treat pain. (The amount and quality of evidence for use of opioids is about the same as the evidence for use of acetaminophen.) (Group 4)

The electronic patient intake form known as PODS – now in development – should be completed, validated and disseminated. (Group 4)

Educational programs for those who prescribe methadone should focus on "skill sets" as well as knowledge. Such programs should be developed by recognized educational providers and should comply with ACCME standards. (Group 4)

Action Steps

Health professions organizations should seek legislation that requires demonstrated knowledge of proper procedures for prescribing controlled drugs in order to qualify for DEA registration (a DEA number). Such knowledge could be demonstrated by successfully completing a CME course (e.g., the buprenorphine model) or by passing an examination. (Group 4)

Medical specialty boards should include a test to assess mastery of guidelines for prescribing opioids (including methadone) in their certification and recertification processes. (Group 4)

Third-party payers should be encouraged to recognize and reimburse for the time required to initiate and manage long-term treatment of chronic pain with opioid medications. Studies have demonstrated that paying for performance changes physician behavior. (Group 4)

CSAT/SAMHSA should:

1. Assign high priority to completion and wide dissemination of the CME course on use of methadone for pain that is now in development. (Group 4)

2. Work with medical specialty societies to disseminate and promote the use of the PODS (Patient-Oriented Drug Screen) computerized questionnaire as soon as it is completed, as well as other validated patient screening questionnaires, to physicians who prescribe methadone and other opioids for pain. (Group 4)

3. Support a recent resolution by the American Academy of Family Physicians, which calls for Federal support of longitudinal studies on the effectiveness of methadone – and all opioids – in the treatment of chronic pain. (Group 4)

4. Convene a "watch dog" group of clinical experts representing medical specialty societies (particularly those in pain and addiction) to monitor the accuracy of information about methadone presented in major websites and other resources used by physicians and pharmacists, and to proactively communicate with the sponsors or publishers to request correction of inaccurate, outdated or confusing information. (Group 4)

Medical Complications and Adverse Drug Events Associated with Methadone

Methadone does not trigger the same level of concern among prescribers as drugs with better-understood risks, such as warfarin or MAO inhibitors. A national survey of OTPs in all 50 states by Krantz et al. (in press) found that fewer than one in four medical directors of OTPs were aware that methadone is associated with medical complications such as torsades de pointes. If physicians were more aware of the potential side effects of methadone, they would manage patients accordingly.

A significant proportion of deaths among methadone users cannot be avoided. Even improved patient education and monitoring will not prevent patients from increasing their doses in an attempt to achieve euphoria or somnolence, or from combining methadone with alcohol or other drugs. Therefore, efforts should focus on addressing those complications that are avoidable.

Strategies

Research: More research is needed to identify specific risk factors for fatal cardiac events in patients taking methadone. Current data are sufficient to support taking actions now that can improve patient safety overall. For example, QT interval is an unreliable predictor of risk, yet ECG screening is the only method currently available to assess the risk of sudden cardiac death in patients who are candidates for methadone. Options for evaluating cardiac risk among patients who are candidates for or using methadone include: (1) admit patients to the hospital and monitor them during treatment; (2) perform serial ECG screening before and after methadone induction (an approach approved by the FDA for LAAM); or (3) perform outpatient ECG screening selectively. (Group 5)

Best Practices: Physicians need to understand methadone's pharmacology and "best practices" for its use, as well as specific indications and cautions to consider when deciding whether to use this medication in the treatment of pain or addiction. In particular, the medical community needs credible information on documented risks associated with use of methadone, as well as guidance in assessing risk-benefit ratios in particular patients.

In some at-risk patients, methadone doses can be reduced or other drugs can be prescribed. In other patients, splitting the methadone dose may be an effective way to reduce cardiac risk. Among users who rapidly metabolize methadone, a split dose lowers the peak exposure to the drug and, in theory, decreases the risk of prolonged QTc. (Group 5)

Clinical guidelines and best practices developed for the use of methadone by OTPs could serve as models for other treatment settings. Compliance with the guidelines could be tied to institutional accreditation. (While this recommendation is relevant to the educational needs of the medical community as a whole, it has particular resonance for staff of opioid treatment programs and physicians who provide pain treatment.) (Groups 3, 5)

Action Steps

Addiction treatment organizations (e.g., ASAM, AOAAM, AAAP, AATOD) should encourage providers to use ECG screening to identify patients who are at increased risk for adverse events associated with methadone. For methadone users who are found to be at high risk for a cardiac event, buprenorphine should be considered as a treatment option. (Group 5)

NIDA should fund clinical studies that attempt to identify specific factors that increase the risk of adverse events associated with methadone. The research evidence should be incorporated into medical education programs, so as to increase physicians' awareness of the risks associated with methadone use. (Group 5)

CSAT/SAMHSA should:

1. Convene a national task force to reach consensus on guidelines for reducing patient risk (perhaps in collaboration with NIDA). Such a task force should focus on whom to screen, which screening protocols to use, thresholds for treatment, and alternative treatment options. (Group 5)

2. Require better methods for collecting and sharing data on methadone-related adverse events and medical complications to clarify the level of risk associated with the use of methadone within accepted dosing guidelines. (Group 5)

3. Consider requiring certification of competency for physicians who prescribe methadone in addiction treatment. (However, care is required to prevent certification from becoming an impediment to use of a valuable medication.) (Group 5)

Role of Regulatory and Enforcement Agencies

The medical community and government agencies share a dual responsibility for ensuring that methadone and related medications continue to be available for therapeutic use, as well as for preventing their misuse or abuse.

Strategies

Collaboration: Potential avenues for enhancing collaboration between regulators and the prescriber community include: prescribing courses offered by Boards of Medicine; CSAT/SAMHSA outreach to medical students and residents; and engagement with physicians in the Veterans Administration health care system. (Group 6)

Professional Education: Better training of physicians in how to prescribe methadone is needed. CSAT/SAMHSA is assisting with development of a CME course on the use of methadone to

treat chronic pain. The course will be launched in September 2007 at the Cleveland Clinic and the New York State Academy of Family Physicians. (Groups 2, 3, 4, 5, 6)

Patient Information: Patients are less likely to use or handle methadone in a risky manner when they are educated about the attendant risks. Patient information needs to be clearer and more accessible to those with limited vision, low literacy skills, etc. (Groups 3, 6)

Action Steps

State Boards of Medicine and other regulatory and enforcement agencies should:

1. Work with medical schools to incorporate knowledge about methadone and other opioids in curricula;

2. Work with residency program directors and residency review committees (RRCs) to incorporate skills training in prescribing methadone and other opioids as part of residency training;

3. Offer online CME courses on prescribing controlled drugs, including methadone (such as the courses CSAT is developing);

4. Adopt FSMB policy statements on the use of opioids to manage pain;

5. Inform licensees about these issues via newsletters and other means of communication;

6. Continue to enforce laws and regulations governing prescribing and to publish information about standards of practice and disciplinary actions for violations; and

7. Expand the use of Prescription Monitoring Programs (perhaps to include patients who need intervention). (Groups 3, 4, 5, 6)

Health professions associations and regulatory/enforcement agencies should:

1. Use newsletters, journals, websites, and annual meetings to raise members' understanding of complex issues such as methadone deaths; and

2. Provide educational opportunities (as the New York State Academy of Family Physicians is doing by offering the new CME course on prescribing methadone for pain). (Groups 3, 4, 6)

Medical and other health professions associations and addiction specialty organizations should:

1. Develop and/or adopt clinical guidelines and educational programs about the management of pain (e.g., as the Federation of State Medical Boards has done); and

2. Endorse better education of physicians about pain and addiction (as called for in a resolution adopted by the FSMB in 2007). (Groups 4, 5, 6)

Pharmaceutical manufacturers and distributors should:

1. Educate physicians about possible adverse effects when detailing a drug;

2. Support the development and dissemination of educational programs through unrestricted grants to accredited providers of continuing education; and

3. Work with patient education organizations to develop patient information about methadone that is clear and accessible to all patients, including individuals with limited vision, low literacy skills, and non-English speakers. (Group 6)

CSAT/SAMHSA should:

1. Continue to work with its group of experts to refine the statement on uniform definitions of methadone-associated death;

2. Collaborate with NAME and SOFT to achieve agreement on a standard nomenclature and criteria for classifying methadone deaths;

3. Continue to collect and refine data on methadone-related deaths;

4. Expand its guidelines for OTPs to emphasize caution during the induction process;

5. Consider whether to require that OTPs operate 7 days a week to eliminate the need for take-home medications;

6. Continue its excellent work in developing CME courses on prescribing methadone and other opioids, and develop additional CME courses as needed;

7. Reach out to medical societies, other health professions associations, and enforcement and regulatory organizations to assure the widest possible audience for its products. (Groups 1, 2, 3, 4, 5, 6)

CLOSING REMARKS BY CSAT DIRECTOR H. WESTLEY CLARK, M.D., J.D., M.P.H., CAS, FASAM

Since the initial 2003 National Assessment meeting in response to the increasing number of methadone-associated deaths, data show that these deaths, as well as all opioid-related deaths, continue to rise. By reconvening experts and representatives of Federal and State agencies, practitioners, patient advocates, and pharmaceutical industry representatives knowledgeable about the issues surrounding methadone mortality, we have reaffirmed our commitment to understand and address these critical issues. The data and perspectives presented during the day-long reassessment meeting were assessed through the prism of the work groups to ensure that our next steps are informed by current research findings, clinical experience, and patient and family viewpoints.

SAMHSA will continue to work collaboratively with our Federal partners DEA and FDA, States, medical societies and organizations, patient advocacy groups, and other interested parties to develop and implement practical action steps that will reduce avoidable methadone-associated deaths. Meeting participants offered many suggestions for consideration by SAMHSA and others. Some of these suggestions reinforce or expand on those made by meeting participants in 2003; others reflect our expanded knowledge and take us in new directions.

SAMHSA is particularly interested in taking a balanced approach to reducing methadone-associated deaths and value the input provided by a full spectrum of groups. With this approach, we intend to focus on key issues and avoid unintended consequences from the policies and actions we pursue. We are now better equipped to recognize the complexity represented by methadone-associated deaths and understand the need for participation of patients, medical professionals, professional organizations, and Federal and State agencies to achieve our goals.

There are multiple initiatives already underway by CSAT, SAMHSA, and others to understand and address methadone-associated deaths. Clearly, there is much more to do to gain an accurate picture of the circumstances that lead to these unfortunate deaths and ways to limit them. This reassessment effort has provided critical data and guidance to SAMHSA as we work to find the best solutions for patients and the field, and to meet our regulatory and public health responsibilities.

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APPENDIX A

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Agenda

Methadone Mortality – A Reassessment

Friday, July 20, 2007
The Madison Hotel, Washington, DC

8:30 – 8:40 a.m.
Welcome and Acknowledgements
Kenneth Hoffman, M.D., M.P.H. (DPT/CSAT/SAMHSA)

8:40 – 9:00 a.m.
Opening Remarks and Charge to the Conferees

H. Westley Clark, M.D., J.D., M.P.H., CAS, FASAM; Director
Center for Substance Abuse Treatment, SAMHSA

9:00 – 10:00 a.m.
Review of Current Information and Trends
Moderator: Moira O'Brien, M.Phil

DEA: ARCOS Data
June E.. Howard, DEA

FDA: Methadone Utilization Data
Laura Governale, Pharm.D., M.B.A..

CDC: Data from the National Center for Health Statistics
Lois Fingerhut, M.A.

SAMHSA: Drug Abuse Warning Network (DAWN)
Elizabeth H. Crane, Ph.D., M.P.H.

10:00 – 10:15 a.m.
Break

10:15 – 11:30 a.m.
Review of Current Information and Trends (continued)
Moderator: Frank Vocci, Ph.D .

RADARS Methadone Study
Richard Dart, M.D., Ph.D.

Methadone-Related Deaths in New England
Marci Sorg, Ph.D.

Methadone-Related Deaths in Texas
Jane C. Maxwell, Ph.D.

Methadone-Related Deaths in West Virginia
Martha J. Wunsch, M..D., FAAP

Methadone-Related Deaths in Florida
Bruce Goldberger, Ph.D., DABFT

11:30 – 12:15 p.m.
Emerging Clinical Concerns
Moderator: Seddon R. Savage, M.D.

Considerations in the Use of Methadone to Treat Addiction
Judith Martin, M.D.

Considerations in the Use of Methadone to Treat Pain
Scott Fishman, M.D.

A Framework for Conceptualizing Diversion of Prescription Drugs
Aaron Gilson, Ph.D.

12:15 – 1:30 p.m.
Lunch (on your own)

1:30 - 3:00 p.m.
Breakout Groups Meet

Group 1: Improving Case Definitions and Classifications
Co-Chairs: Bruce Goldberger, Ph.D., DABFT and Marci Sorg, Ph.D.

Group 2: Improving Data Collection and Analysis
Co-Chairs: Jane C. Maxwell, Ph.D., and Nina Shah, Ph.D.

Group 3: Strategies for Reducing Methadone Deaths Associated with Addiction Treatment
Co-Chairs: Mark Parrino, M.P.A. and Joan Zweben, Ph.D.

Group 4: Strategies for Reducing Methadone Deaths Associated with Pain Treatment
Co-Chairs: Margaret Kotz, D.O. and Howard A. Heit, M.D., FASAM

Group 5: Medical Complications Associated with Methadone Use
Co-Chairs: Stephen Cantrill, M.D., FACEP, and Mori J. Krantz, M.D.

Group 6: The Role of Regulatory and Law Enforcement Agencies
Co-Chairs: William Harp, M.D., and Charles Cichon

3:00 – 3:15 p.m.
Break

3:15 – 4:15 p.m.
Reports from the Breakout Groups (10 minutes each)
Moderator: Kenneth Hoffman, M.D., M.P.H.

4:15 – 5:00 p.m.
Discussion and Action Planning: Do the data show an increase in methadone-associated deaths? What factors are involved? What can be done about the problem?
Presiding: H. Westley Clark, M.D., J.D., M.P.H., CAS, FASAM

5:00 p.m.
Meeting Adjourns

APPENDIX B

Methadone Mortality – A Reassessment

Friday, July 20, 2007
The Madison Hotel, Washington, DC

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