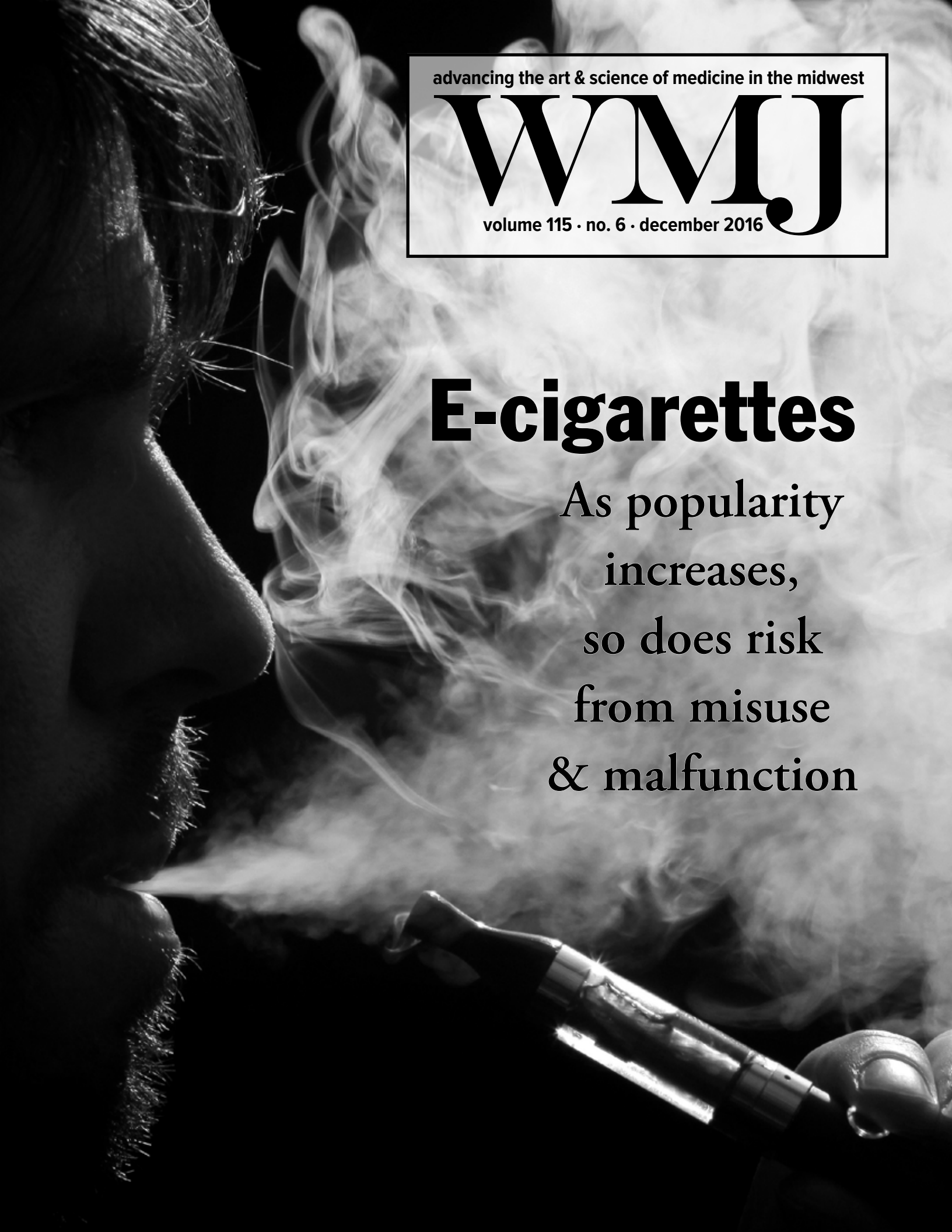
advancing the art & science of medicine in the midwest

WMJ

volume 115 · no. 6 · december 2016



E-cigarettes

As popularity increases, so does risk from misuse & malfunction

MORE INSIGHT

helps you make the most of your practice's revenue cycle.

KNOW YOU HAVE A DEDICATED BANKER WHO UNDERSTANDS YOUR INDUSTRY AND YOUR NEEDS.

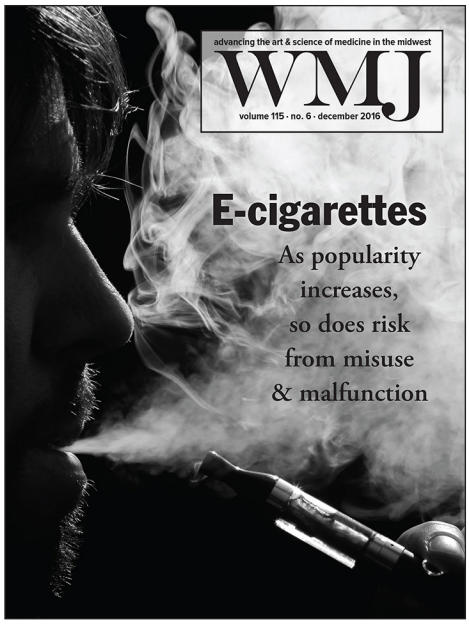
As a healthcare professional, you want to spend more time helping patients and less time worrying about your finances. With dedicated Healthcare Business Bankers, PNC provides tools and guidance to help you get more from your practice. The PNC Advantage for Healthcare Professionals helps physicians handle a range of cash flow challenges including insurance payments, equipment purchases, and managing receivables and payables. In such a fast-moving business, PNC understands how important it is to have a trusted advisor with deep industry knowledge, dedication and a lasting commitment.

ENSURE ACCESS TO CREDIT | ACCELERATE RECEIVABLES | IMPROVE PAYMENT PRACTICES | MONITOR & PROJECT CASH | PURSUE FINANCIAL WELL-BEING

PNC | CFO℠
Cash Flow Optimized

Call a Healthcare Business Banker at 877-566-1355 or go to pnc.com/hcprofessionals

PNC BANK



COVER THEME
E-cigarettes

As their popularity increases, so does risk from misuse and malfunction. A report in this issue of *WMJ* examines the increase in frequency of e-cigarette exposure calls to the Wisconsin Poison Center, and calls for strategies to prevent future poisings, including warning labels and public advisories to keep patients safe.

Cover design by Kendi Parvin

Volume 115, no. 6 • December 2016

WMJ

advancing the art & science of medicine in the midwest

EDITORIAL

ORIGINAL RESEARCH

The mission of *WMJ* is to provide a vehicle for professional communication and continuing education for Midwest physicians and other health professionals. *WMJ* is published by the Wisconsin Medical Society.

The *WMJ* (ISSN 1098-1861) is published by the Wisconsin Medical Society and is devoted to the interests of the medical profession and health care in the Midwest. The managing editor is responsible for overseeing the production, business operation and contents of the *WMJ*. The editorial board, chaired by the medical editor, solicits and peer reviews all scientific articles; it does not screen public health, socioeconomic, or organizational articles. All articles published herein, including commentaries, letters to the editor, and editorials represent the views of the authors, for which neither *WMJ* nor the Wisconsin Medical Society take responsibility, unless clearly stated. Advertising content is the responsibility of the advertiser and does not imply an endorsement or sponsorship by *WMJ* or the Wisconsin Medical Society and its affiliates unless specified. *WMJ* is indexed in Index Medicus, Hospital Literature Index, and Cambridge Scientific Abstracts.

Send manuscripts to *WMJ*, 330 E Lakeside St, Madison, WI 53715. Instructions to authors are available at www.wmjonline.org, call 866.442.3800, or e-mail wmj@wismed.org.

SUBSCRIPTION RATES
Members: included in membership dues.
Non-members: $149. Current year single copies, $25 each. Previous years' single copies, when available, $12 each.
Periodical postage paid in Madison, Wis, and additional mailing offices.
Published every other month, beginning in February.
Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917.
Authorized August 7, 1918.
Address all correspondence to WMJ, PO Box 1109, Madison, WI 53701. Street address: 330 E Lakeside St, Madison, WI 53715;
e-mail: wmj@wismed.org

POSTMASTER
Send address changes to: *WMJ*,
PO Box 1109, Madison, WI 53701

ISSN 1098-1861
Established 1903

REVIEW ARTICLE

BRIEF REPORT

CASE REPORT

YOUR PROFESSION

YOUR PRACTICE

Comments on Treatment: Frostbite and Allied Conditions

Editor's note: The following editorial was published in WMJ*, Volume 41, No. 1, p. 46, January 1942*

In peacetime only the physician in northern rural climates is apt to see more than an occasional case of frostbite. In wartime with men stationed in cold climates, the subject assumes great importance, and it behooves the physician to become familiar with its prevention and treatment. We can learn much from the experience of the English, and this article is based on a recent paper of Greene which appeared in *Lancet* (December 6, 1941).

There are various types of frostbite. The most familiar is the sudden frostbite of which the "nipped ear" is the most common example. The gradual frostbite in which the painful sensation of extreme cold gives way to a pleasant numbness is more serious since the damage to tissues is much more extensive. On thawing a flush surrounds the frozen area and invades it. Swelling due to transudation follows, and if the damage is severe, blood may escape into the injured tissue causing it to appear dark blue.

"Trench foot" can be considered a form of gradual frostbite, although it is usually produced by a temperature that is above freezing. It is now recognized that dampness, constriction and stagnation of circulation, fatigue, and malnutrition are important contributory factors. Likewise the new entity, "shelter foot," (a swelling of the feet of one who spent the night in a sitting position without compensatory rest in a horizontal position during the day) has as its main causative factor venous stagnation and possibility increased capillary permeability. A third form, namely "immersion-foot" is seen in men who have been forced to spend a long time in waterlogged boats.

Much can be done to prevent frostbites. The need for adequate clothes is obvious, and the importance of dry socks especially must be emphasized. In the last war it was found that rapid marches just before the men entered the trenches were particularly prone to cause "trench foot." Sleeping in the sitting position and standing motionless for a long time leads to venous stagnation and thus predisposes to frostbite. The need for exercising the muscles of the leg while standing is to be emphasized. Much foot trouble can be avoided by gently massaging the feet with whale or other types of animal oil. The wearing of rubbers or rubber boots when it is necessary to stand or work in cold mud has been found very effective in reducing "trench foot." The nutritional state is also an important factor and an adequate supply of citrus fruit is undoubtedly beneficial since it prevents capillary hyperpermeability.

In the treatment of frostbite two things must be avoided: excessive warmth and undue friction or rubbing. The frostbitten part must be kept cool and gentle warmth be applied very slowly. Rubbing beyond the stage of very mild massage can only cause destructive damage and increase the danger of infection.

The seriousness of frostbite must be constantly kept in mind. If the feet are involved, the patient should be transported by stretcher, and if the hand or arm is frozen, the affected part must be carried in a sling. It is advisable to paint the part with a nonirritating antiseptic solution and to cover it with sterile dressings. Complete rest of the traumatized part is essential. It is advisable to give antitetanic serum. Supportive treatment, hot foods and drinks, and warmth to the unaffected parts of the body are helpful.

Hasty amputations should be avoided except in cases of spreading and uncontrolled sepsis. It is surprising how often a foot or a hand can be saved that appeared discouragingly bad and hopeless.

—A.J. Quick, MD, editor

Telling a Clinical Story: The Role of Case Reports in a General Journal

John J. Frey III, MD, Medical Editor

As recently as the 1950s, most journals weren't publishing what we have come to expect as research. Sir Austin Bradford Hill published the first randomized clinical trial in 1948. Until the 1960s, the bulk of articles published in major journals were case series and case reports and opinion pieces by notable academics. The emphasis over the past 25 years on methodological rigor and clinical evidence has dramatically improved the reliability and reproducibility of research published in scholarly journals such as the *WMJ*. Reviewers are skilled at recommending improvements in methods and analysis required to make an article more widely valuable. So where did that leave case reports?

In the past decade, case reports have become more common—again—and there are even whole journals devoted to case reports. The number of venues is growing. I review journals for possible inclusion in PubMed Central and almost all of them, regardless of the scope of the journal, include case reports. The quality can vary tremendously, but scholarly case reports and case series continue to be an important source of information for clinical care and research.

Over the past decade, about a quarter of the articles published in *WMJ* have been case reports or case series. Readers enjoy them, and case reports are often the first step for a young author on his or her way to an academic career. Excellent online guidelines for structure and organization exist,[1] but I'd like to offer a few additional suggestions for authors seeking to make their case report stronger before submitting it for consideration in *WMJ*.

Preparing to Submit a Case Report

The case should be one that is not so arcane or specialized that it would not be useful to the wide readership of the journal.[2] Many times, such cases are better suited to a specialty or subspecialty journal. That decision should be made by the authors before they submit a manuscript to a journal by reading previous issues of the *WMJ* to see whether the subject would be a good fit or sometimes directly by corresponding with the editor. Since many case reports in *WMJ* are collaborations between physicians-in-training and senior faculty members, we rely on those senior people to make sure the case is well written and organized and would be of interest to the *WMJ* audience.

Authors should spend time comprehensively reviewing the literature for the discussion section of the case report. Authors should avoid terms like "very little has been written" or labeling something as unique. Human beings are unique but diseases aren't. A well written discussion serves as review of a general topic, points out what is new or different about the case being presented, and reports controversies and differences of opinion about either diagnosis or management. The number of references is not as important as the timeliness and depth of those references.

Finally, case descriptions should include more than simply the laboratory data and course of the disease or condition. Cases are stories about patients who live in a context, not in a neutral space. Socioeconomic data about the patient—or "case"—are often omitted, yet are essential to understanding whether a clinical story has applicability to one's practice. Of course authors should be careful about confidentiality, but all clinicians recognize the importance of social determinants of health to clinical care. We will be asking authors to bring more narrative about the patient into the case, including intermediate or long-term follow-up that addresses the clinical and social issues in the case. Readers need to know more about the next chapter in the story.

Socioeconomic data about the patient – or "case" – are often omitted, yet are essential to understanding whether a clinical story has applicability to one's practice.

One of my favorite residency stories concerned the morning report that the distinguished chair of my department ran every Monday. I had come to town as a fairly cocky second-year resident and stood up to do my

first case presentation. I started by saying "the patient is a 50-year-old black male who…." and was interrupted from the back of the room by the chair who loudly asked, "Black male what?" stopping me in my tracks. I didn't know what he was asking and then he said "black male Labrador retriever, black male cockatoo?" and went on to say that he was a black MAN. I then proceeded into the case and he stopped me again. "Is he married? Does he work? Where does he live? What is his life like? All that is important!" That was 45 years ago but changed the way I did case presentations for the rest of my life.

A "traditional" case report is often a disease review scrubbed of anything important about the patient's life that truly might affect management or outcome. Packer and colleagues make the case for a patient-centered narrative—what they call a "hybrid narrative"—that contains information about the patient's life as well as the patient's disease as a better method for students to learn from case reports.[3]

Adding Clinical Narrative to a Case Report

We would like authors to start case reports with what was called a patient profile, when the problem-oriented medical record was first introduced. The profile should be brief but contain relevant patient social history that might have a bearing on the case and the outcome. Good clinicians don't compartmentalize social history, narrative, and clinical data either when they see patients or teach. The biopsychosocial model that George Engel wrote about in the 1970s integrates those components in clinical care and research. That integration should be reflected in the medical literature. For example, in an article about suicide in the elderly, the two cases begin, "Mrs C, aged 88, was the sole carer of her frail older husband. She was a retired typist and then homemaker. Her two daughters lived overseas." and "Mr B, aged 89, was a retired businessman and widower of 30 years who lived alone. He had 2 children who lived interstate."[4] At the beginning of the case, we know something about these patients that is central to their reason for being admitted and that will be challenges post discharge.

In this issue of *WMJ*, in a well-written, informative case describing a life-threatening complication of one of the newer diabetic medications,[5] Rebedew begins the case with "A 34-year-old white man with chronic alcohol abuse came into clinic for follow-up of his hospitalization for alcohol intoxication, hyponatremia, hypokalemia, and hypophosphatemia." The introduction is written in a traditional fashion and sets the stage for a complex management process over a long hospitalization.

However, if one were to apply some of the narrative criteria that we would like to see in future case reports, the author might have included something about the man's social situation, living situation, work status, and even something about his education, and level of function. The patient is a person with a complicated life, not just a complicated medical problem. Writing, for example—and this is fiction on my part—that "A 34-year-old, separated, father of 2 young children, who is trained as a carpenter but has been unable to maintain a job over the past year in part because of chronic alcohol abuse, is currently living with friends and came into the clinic for follow up…" alerts readers to the challenges beyond the biological that face the care team. It also demands that, at the end of the narrative of the patient's hospitalization, the authors would have to address something in addition to, "subsequently, he was transferred out of the ICU and discharged home 3 days later, performing all of his activities of daily living," and say something about finding him a stable living situation and entering an alcohol rehab program in the community.

If case reports—and case presentations at hospital rounds, clinic rounds or morning reports—are to be teaching opportunities about how to think about and approach clinical care,[6] leaving out important psychosocial issues in discussing and writing about the case leave students and residents with the impression that "cases" are separate from the patients who are the sources of that story. There is an old quote that "statistics are human beings with the tears washed off." So cases should not be clinical narratives with the person left out.

REFERENCES

1. Case Report Writing. http://www.care-statement.org/case-report-writing-template.html. Assessed December 20, 2016.

2. Frey JJ 3rd. The Advantage of a General Journal. *WMJ*. 2015 Aug;114(4):129-130.

3. Packer CD, Katz RB, Iacopetti CL, Krimmel JD, Singh MK.A Case Suspended in Time: The Educational Value of Case Reports. *Acad Med.* 2016 Apr 19. [Epub ahead of print.]

4. Wand AP, Peisah C, Draper B, Jones C, Brodaty H. Rational Suicide, Euthanasia, and the Very Old: Two Case Reports. *Case Rep Psychiatry*. 2016;2016

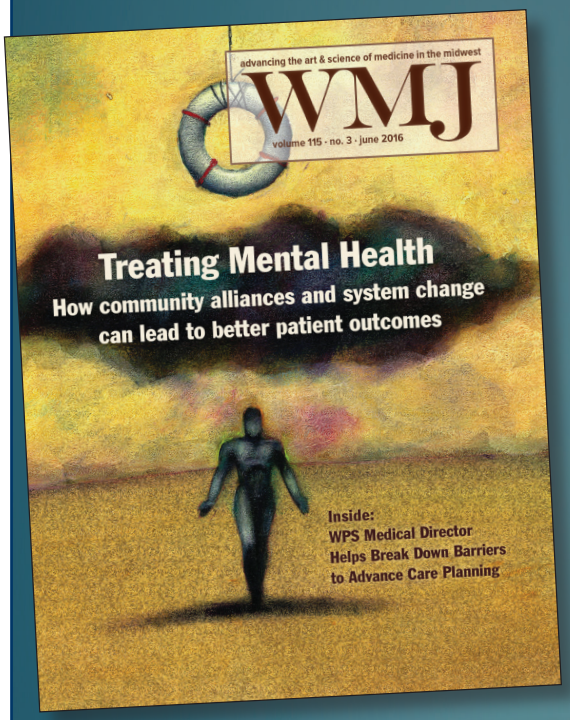
5. Rebedew, DL. Is Central Pontine Myelinolysis Reversible? *WMJ*. Dec. 2016; 115(6);326-328.

6. Florek AG, Dellavalle RP. Case reports in medical education: a platform for training medical students, residents, and fellows in scientific writing and critical thinking. *J Med Case Rep.* 2016 Apr 6;10:86. doi: 10.1186/s13256-016-0851-5.

advancing the art & science of medicine in the midwest

WMJ

CALL FOR PAPERS & REVIEWERS



Since 1903, *WMJ* has served as a forum for professional communication and continuing education for physicians and other health professionals. This tradition continues today, but with a broader focus that extends across the country and even around the world.

Published six times a year, *WMJ* is a peer-reviewed, indexed scientific journal available via printed subscription and in full text online at www.wmjonline.org and PubMed through the National Library of Medicine.

WMJ invites original research, case reports, review articles, essays and "health innovations"—short reports that showcase the results of initiatives being tested to improve quality, patient safety and satisfaction, cost efficiency and more in clinics and communities throughout the Midwest.

WMJ also seeks health care professionals who can be objective and insightful to add to our list of highly qualified reviewers.

Become part of the tradition: submit a manuscript, serve as a reviewer and become a reader.

Visit www.wmjonline.org or e-mail wmj@wismed.org for manuscript submission guidelines and tips for authors and reviewers, or to access *WMJ* online.

Neonatal Abstinence Syndrome and Maternal Substance Use in Wisconsin, 2009-2014

Karina A. Atwell, MD, MPH; Harold B. Weiss, PhD, MPH, MS; Crystal Gibson, MPH; Richard Miller, MS; Timothy E. Corden, MD

ABSTRACT

Introduction: Increasing rates of neonatal abstinence syndrome (NAS), most commonly linked to maternal opioid use, are a growing concern within clinical and public health domains.

Objectives: The study aims to describe the statewide burden of NAS and maternal substance use, focusing on opioids in Wisconsin from 2009 to 2014.

Methods: Trends in NAS and maternal substance use diagnosis rates were calculated using Wisconsin's Hospital Discharge Data. Demographic and payer characteristics, health service utilization, and clinical outcomes were compared for newborns with and without NAS. Demographic and payer characteristics were compared between women with and without substance use identified at time of delivery.

Results: Rates of NAS and maternal substance use, most notably opioid use, increased significantly between 2009 and 2014. The majority of newborns diagnosed with NAS, and women identified with substance use, were non-Hispanic, white, and Medicaid-insured. Disproportionate rates of NAS and maternal opioid use were observed in American Indian/Alaska Native and Medicaid populations compared to white and privately insured groups, respectively. Women age 20-29 years had the highest rates of opioid use compared to the reference group (10-19 years). Odds of adverse clinical outcomes and levels of health service utilization were significantly higher for newborns with NAS.

Conclusions: Similar to trends nationally, our findings show an increase in maternal opioid use and NAS rates in Wisconsin over time, with disproportionate effects in certain demographic groups. These findings support the need for targeted interventions in clinical and public health settings aimed at prevention and burden reduction of NAS and maternal substance use in Wisconsin.

• • •

Author Affiliations: University of Wisconsin School of Medicine and Public Health, Madison, Wis (Atwell), Bureau of Community Health Promotion, Division of Public Health (DPH), Department of Health Services (DHS), Madison, Wis (Weiss, Corden); DPH, DHS (Gibson), Office of Health Informatics, DPH, DHS (Miller).

Corresponding Author: Karina Atwell, MD, MPH, University of Wisconsin School of Medicine and Public Health Preventive Medicine Residency Program, 750 Highland Ave, Rm 4263 HSLC, Madison, WI 53705; phone 608.695.0581; fax 608.265.3286; e-mail KAtwell@uwhealth.org.

CME available. See page 294 for more information.

BACKGROUND

The use of drugs during pregnancy, both illicit and prescribed, can lead to negative consequences for mothers and newborns. Of particular concern amidst the current epidemic of opioid use and abuse in the United States is the increasing number of infants born with physical dependence to opioids taken by the mother.[1-4] Known as neonatal abstinence syndrome (NAS), this condition encompasses a constellation of behavioral and physiological signs and symptoms characterized by neurological over-activity, feeding difficulties, and respiratory problems, which can result in significant medical treatment, prolonged hospital stays, and increased costs in the days and weeks following birth.[5] Clinical manifestations of NAS depend on various factors influencing the newborn's intrauterine drug exposure, including the type, dose, frequency, and metabolism of the drug used by the mother.[6] In addition to NAS, these newborns experience higher rates of prematurity and poor fetal growth.[1,3-6] There is also evidence of increased risks for certain birth defects and associated neurobehavioral and developmental problems later into childhood.[7,8]

NAS can result from in utero exposure to prescription opioid pain medications, heroin, methadone, and buprenorphine used for opioid addiction treatment, benzodiazepines, barbiturates, amphetamines, cocaine, marijuana, and alcohol.[6,9] The 2012-2013 National Survey on Drug Use and Health reported that 5.4% of pregnant women age 15 to 44 years old used illicit drugs.[10] Opioid use during pregnancy rose nearly 2.5-fold between 2001 and 2009 within a nationally representative sample of inpatient hospital discharges.[11] Looking at all women reproductive age, on average 27.7% of privately insured and 39.4% of Medicaid-enrolled women filled a prescription for an opioid

pain medication annually in 2008-2012.[12] Given that negative effects of substance exposure can occur during the unrecognized first weeks of pregnancy, and that half of all US pregnancies are unplanned, the growing use and misuse of opioids in women of reproductive age presents potential risks for mother and infant.[13]

Previous reports indicate that Wisconsin's rates of opioid prescribing, use, and abuse are similar to rising national trends.[14] To date, quantification of NAS and maternal substance use in the state has been limited. The objectives of this study are to describe the statewide burden of NAS in Wisconsin from 2009 to 2014, including perinatal outcomes, hospital utilization trends, and differences across demographic and payer groups between newborns with and without a NAS diagnosis, and to describe the statewide burden of maternal substance use identified at time of delivery in Wisconsin from 2009 to 2014, including differences across demographic and payer groups comparing mothers identified with and without substance use.

METHODS

Data Source

Wisconsin's inpatient Hospital Discharge Data (HDD) was used to identify maternal delivery hospitalizations and hospitalizations of newborns up to 28 days after delivery in Wisconsin facilities from 2009 to 2014. The HDD contains all hospital admission-discharge encounters for facilities located in Wisconsin and includes demographic information for patients, procedure and diagnosis codes, length of hospital stay, discharge status, and billing information (eg, payer and hospital charges). Delivery hospitalizations among newborns and mothers were analyzed separately. Hospitalization records for Wisconsin residents receiving care in a neighboring state and within federal Veterans Affairs hospitals are not included in the inpatient HDD.

This study used nonidentifiable patient data and was considered exempt per the Wisconsin Department of Public Health Institutional Review Board criteria.

Study Population

Newborns—Newborn hospitalizations (referred to as newborns in subsequent text) with a NAS diagnosis were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis code 779.5 (drug withdrawal syndrome in newborn). Newborns were included if they were age 0-28 days at the onset of hospitalization; a range chosen based on current knowledge of possible withdrawal symptom onset for the substances most commonly associated with NAS.[6] The 0-28 day timeframe allowed for capturing newborns experiencing NAS shortly after birth and those who presented with NAS after being discharged.

Neonatal abstinence syndrome can occur due to iatrogenic causes from hospital therapies required for other complications in the newborn period unrelated to maternal drug use. Based on a 2012 study by Patrick et al, newborns with select diagnoses associated with iatrogenic causes of NAS were excluded. These included very low birth weight (<1,500g, ICD-9-CM 765.0, 764.01-764.05, V213.1-V213.3), gestational age less than 24 weeks (ICD-9-CM 765.21), intraventricular hemorrhage (ICD-9-CM 772.1), periventricular leukomalacia (ICD-9-CM 779.7), necrotizing enterocolitis (ICD-9-CM 777.5), spontaneous intestinal perforation (ICD-9-CM 777.6), or bronchopulmonary dysplasia (ICD-9-CM 770.7).[1]

The comparison group of newborns without NAS included newborns born within, or en route to, the hospital during the study timeframe. The same exclusion criteria for iatrogenic causes of NAS were applied to this population to ensure comparable groups.

Delivering Mothers—Delivery hospitalizations (referred to as mothers in subsequent text) with a live birth were identified using methods described by Kuklina et al.[15] Any record containing delivery-related procedure codes (V 720-1, V724, V726, V729, V736, V740-2, V744, V7221, V7229, V7231, V7239, V7251, V7253-54, V7271, V7279, V7322, V7359, or V7499), Medicare Severity Diagnosis-Related group codes (765-768 and 774-775 or ICD-9-CM code 650) were included. Encounters with abortive or abnormal pregnancy outcome codes (ICD-9-CM 630.x, 639.x, 750.x, 690.1x, 695.1x, and 749.1x) were excluded to ensure capture of only live births.

Measures

Newborn Substance Exposure—The ICD-9-CM does not allow for identification of a specific substance of exposure within the 779.5 NAS code. Therefore, newborn substance exposure type was identified by searching for codes associated with a specific drug exposure in the newborn's hospital record.[3] If a substance exposure code was identified without a concurrent diagnosis of NAS, the newborn was excluded as a NAS case due to limitations in confirming if the newborn suffered clinical symptoms meeting criteria for NAS.

Maternal Substance Use—Maternal substance use was captured by searching for select ICD-9-CM codes associated with maternal substance use identified during the delivery hospitalization, mirroring the technique used by Creanga et al.[3] Mothers were classified broadly as substance-using (any substance) or non-substance using. Substance-using mothers included those with ICD-9-CM codes in the hospitalization record for broad drug types, eg, opioid (including heroin, methadone, and opioid analgesic), psychotropic (sedative, hypnotic, and tranquilizers), stimulant, cocaine, cannabis, alcohol, tobacco, other, unspecified, and polydrug. Illicit versus prescribed use could not be ascertained with ICD-9-CM coding.

Demographic Characteristics—Newborn demographic data examined included race, ethnicity, and sex. Maternal demographic data examined were race; ethnicity; and age, categorized as 10-19, 20-29, 30-39, and 40-45 years. Race was classified as white, black, American Indian/Alaska Native, and Asian or Pacific Islander. Ethnicity classification was Hispanic or non-Hispanic. Race and ethnicity were presented separately due to a large proportion of missing race or ethnicity data for some outcomes.

Payer Source—Primary payer for each hospitalization was categorized as private, Medicaid, or other (self-pay, Medicare, or uninsured).

Newborn Health Care Utilization—Two measures were collected: length of stay (LOS) and total hospital charges, defined as the total facility fee reported within the hospital discharge record.

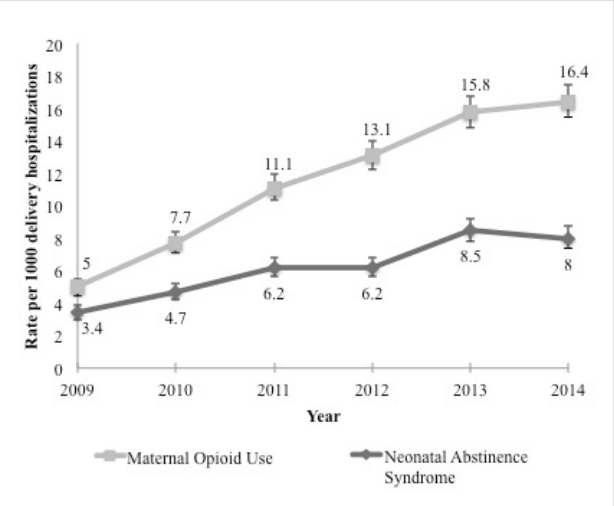
Newborn Clinical Outcomes—Five outcomes were examined: low birth weight (1500g-2500g; ICD-9-CM 764.0-764.2, 764.9, 765.0-765.1), prematurity (24-37 weeks gestation; ICD-9-CM 765.1-765.2), feeding difficulties (ICD-9-CM 779.3), respiratory distress syndromes (ICD-9-CM 769, 770), and seizures (ICD-9-CM 779.0, 780.3).[1,3,16] The HDD does not provide a continuous measure of birth weight, thus this outcome was treated as a dichotomous variable.

Statistical Analysis

NAS rates were calculated by year as the rate of NAS diagnoses per 1,000 delivery hospitalizations. A chi-squared test for linear trend was used to examine significant trends over time. Descriptive statistics for demographic characteristics and payer source were generated for newborns with and without a diagnosis of NAS, and mothers with substance use, opioid use, and no substance use. For newborns, rates of NAS per 1,000 delivery hospitalizations were calculated within each demographic group, and rate ratios (RR) were computed using a reference group within each demographic or payer category. Logistic regression was used to examine adverse clinical outcomes in newborns with NAS compared to newborns without NAS. For continuous health care utilization measures (LOS and total charges), the groups were compared using Student's t-test for continuous variables.

Maternal substance use and opioid use rates were calculated by year as the rate of mothers with substance or opioid use identified at time of delivery per 1,000 delivery hospitalizations. A chi-squared test for linear trend was used to examine significant maternal substance and opioid use trends over time. Rates of any substance use and of opioid use per 1,000 delivery hospitalizations were calculated for each demographic and payer group. Rate ratios were computed using a reference group within each demographic and payer category. *P*-values of 0.05 were considered statistically significant for all comparisons and statistical tests. All analyses were conducted in SAS 9.4. (SAS Institute Inc, Cary, Noarth Carolina).

Figure 1. Rate of Neonatal Abstinence Syndrome and Maternal Opioid Use Among Delivery Hospitalizations in Wisconsin, 2009-2014



95% confidence interval displayed.

RESULTS

Newborn Results

A total of 2,361 newborns were diagnosed with NAS between 2009 and 2014. The rate of NAS per 1,000 delivery hospitalizations increased significantly during this time period (*P* for trend <0.05), Figure 1. Ninety-two percent (n=2182) of NAS cases were diagnosed during the delivery hospitalization. ICD-9-CM codes for a specific substance of exposure were identified in only 17.4% (n=412) of NAS-affected newborns. Of these identified exposures, opioids comprised 70.9% of cases.

Mean LOS for newborns diagnosed with NAS was significantly longer compared to newborns without NAS (16.4 days, SD=16.1 vs 2.8 days, SD=4.9, *P*<0.001). Mean hospital charges were also significantly higher for newborns diagnosed with NAS compared to unaffected newborns ($44,929, SD=58,971 vs $5,864, SD=22,644, *P*<0.001).

NAS rates by demographic and payer group are presented in Table 1. The majority of newborns with a NAS diagnosis were non-Hispanic (73.8%), white (68.2%), and Medicaid-insured (82.0%). Rates of NAS were higher in males and non-Hispanic newborns. Compared to white newborns, the NAS rate was lower in black and "other" race categories, but higher in American Indian/Alaska Native newborns. Compared to privately insured newborns, the NAS rate was higher for Medicaid and other-insured groups.

The proportion of newborns with and without NAS experiencing adverse clinical outcomes is presented in Table 2. Compared to newborns without a NAS diagnosis, newborns with NAS had significantly higher odds of low birth weight, prematurity, feeding difficulties, seizures, and respiratory distress syndrome.

Table 1. Demographic Characteristics and Payer Source for Delivery Hospitalizations of Newborns With and Without Neonatal Abstinence Syndrome (NAS) in Wisconsin, 2009-2014

	Delivery Hospitalizations Without NAS No. (%)	Delivery Hospitalizations With NAS No. (%)	NAS Rate Per 1,000 (95% CI)	Rate Ratio[a] (95% CI)
Sex[b]				
Female	188,589 (48.8)	1,030 (43.6)	5.4 (5.1, 5.7)	Ref
Male	198,014 (51.2)	1,331 (56.3)	6.7 (6.3, 7.1)	1.2 (1.1, 1.3)
Ethnicity[c]				
Non-Hispanic	285,121 (75.0)	1,772 (73.8)	6.2 (5.9, 6.5)	Ref
Hispanic	27,403 (4.6)	109 (7.1)	4.0 (3.3, 4.7)	0.6 (0.5, 0.8)
Race[d]				
White	258,773 (66.9)	1,612 (68.2)	6.2 (5.9, 6.5)	Ref
Black	33,757 (8.7)	162 (6.9)	4.8 (4.1, 5.5)	0.8 (0.7, 0.9)
Asian/Pacific Islander	13,279 (3.4)	8 (0.3)	0.6 (0.2, 1.0)	0.1 (0.0, 0.2)
American Indian/Alaskan Native	3,936 (1.0)	76 (3.2)	18.9 (14.6, 23.2)	3.1 (2.4, 3.9)
Other	18,279 (4.7)	68 (2.9)	3.7 (2.8, 4.6)	0.6 (0.5, 0.8)
Payer				
Private insurance	207,528 (53.7)	294 (12.4)	1.4 (1.2, 1.6)	Ref
Medicaid	161,089 (41.7)	1,938 (82.0)	11.9 (11.4, 12.4)	8.4 (7.4, 9.5)
Other	18,012 (4.7)	129 (5.5)	7.1 (5.9, 8.3)	5.0 (4.1, 6.2)

[a]Rate ratios represent the rate of NAS in each group compared to the rate of NAS in the reference group
[b]Missing for 26 delivery hospitalizations (<0.5%).
[c]Missing for 74,585 delivery hospitalizations (19.1%).
[d]Missing for 59,040 delivery hospitalizations (15.2%).

Table 2. Proportions and Odds of Clinical Outcomes for Delivery Hospitalizations of Infants with NAS in Wisconsin, 2009-2014

	Delivery Hospitalizations Without NAS No. (%)	Delivery Hospitalizations With NAS No. (%)	Rate Ratio[a] (95% CI)
Low birth weight	18,981 (4.9)	349 (14.8)	3.4 (3.0, 3.8)
Prematurity	27,983 (7.2)	411 (17.4)	2.7 (2.4, 3.0)
Feeding difficulties	14,257 (3.7)	470 (19.9)	6.5 (5.9, 7.2)
Seizures	389 (0.1)	21 (0.9)	8.9 (5.7, 13.8)
Respiratory distress syndrome	31,815 (8.2)	677 (28.7)	4.5 (4.1, 4.9)

[a]Odds ratios represent the odds of a clinical outcome for NAS.

Maternal Results

Rates of any substance use per 1,000 delivery hospitalizations increased from 83.0 in 2009 to 96.5 in 2014. Tobacco was the leading substance identified (mean 4814 users per year [range 4658-5015]), followed by opioids, polydrug (defined as >1 substance), cannabis, unspecified substances, cocaine and alcohol (Figure 2). Opioid use rates per 1,000 delivery hospitalizations increased 3.3-fold over the study period (Figure 1, *P* for trend <0.001). Rates of cannabis and polydrug use were the only other substance categories to increase between 2009 and 2014, and to a smaller degree than opioids, 2.1-fold and 2.0-fold, respectively.

Maternal substance and opioid use rates by demographic and payer groups are presented in Table 3. The majority of women with any substance use were non-Hispanic (93.4%), white (79.5%), and Medicaid-insured (70.2%). Compared to women age 10 to 19, the rate of any maternal substance use was higher in women age 20 to 29, and lower in women age 30 to 39 and age 40 to 55 years. Compared to white women, rates of any maternal substance use were higher in black and American Indian/Alaska Native women, but lower in Asian/Pacific Islander and "other" race women. Medicaid-insured and "other"-insured women had higher rates of any maternal substance use versus privately insured women. Similar comparisons of rates between demographic groups were observed for maternal opioid use with the exception of age. Compared to the reference age group (10 to 19 years), the rate of maternal opioid use was higher in women age 20 to 29, and also in women age 30 to 39 and 40 to 55 years.

DISCUSSION

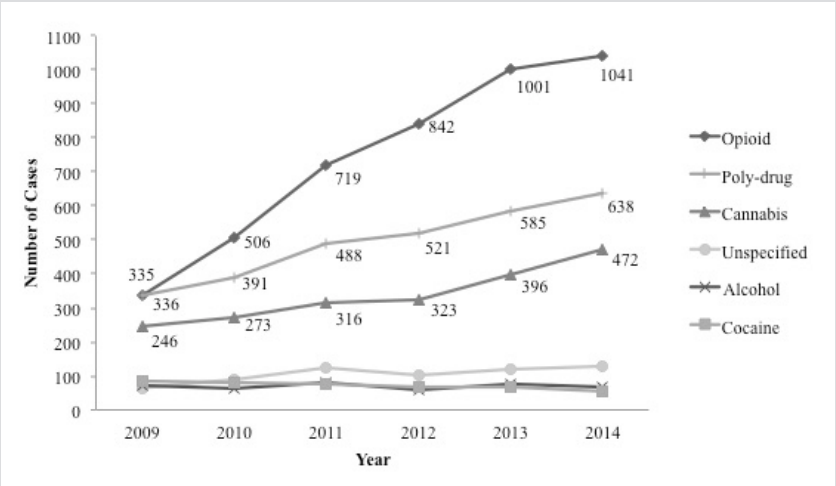
This study found increasing rates of NAS and maternal substance use, particularly for opioids, in Wisconsin between 2009 and 2014. Although analyzing mothers and newborns separately restricts causal inferences, the parallel rising trends for both findings is supportive of an association. There was a slight decline in the NAS rate in 2014; however, this was not statistically different from the rate in 2013. The decline could represent a true plateau in the number of cases or be an outlier within a continued upward trend. It also might signal improvements in the prenatal management of substance-using mothers, in particular given the 4% rise in maternal opioid use rates observed from 2013 to 2014.

The higher incidence of poor perinatal outcomes in newborns with NAS certainly contributes to the observed increased health service utilization for these newborns. These adverse outcomes must be interpreted cautiously. Some outcomes measured are clinical criteria used within symptom scoring tools to make a diagnosis of NAS, and therefore are expected to be more common in newborns with this diagnosis.[5,6] Causal links between poor clinical outcomes and substance use by the mother should be considered within the context of other potential confounding risk factors, which were not explored in the present analysis. These include

the impact of other clinical conditions from which the newborn may be suffering, as well as maternal factors such as stress, other substances used, general health, mental health disorders, socioeconomic status, and characteristics of prenatal care, which could contribute to poor newborn outcomes.[16,17]

The study's findings support anecdotal reports of increasing NAS and maternal opioid use observed by clinical and public health practitioners across the state. Further, the analysis highlights populations with the highest burden of NAS and maternal substance use (eg, non-Hispanic, White, and Medicaid-insured newborns and women), while identifying subgroups disproportionately affected by these issues (eg, American Indian and Alaska Native, non-Hispanic, and Medicaid-insured newborns and women; women aged 20-29 years old). Wisconsin's findings are comparable to descriptive analyses from other states, including Tennessee, Ohio, Washington, and Florida, suggesting a need for additional research, prevention and treatment investments, and nonpunitive policy initiatives targeting substance exposure during pregnancy and associated impact on newborns at the state and national levels.[1,3,9,17,18]

Figure 2. Maternal Substance Use Identified During Delivery Hospitalization in Wisconsin, 2009-2014



Tobacco use not shown due to scale.
Hallucinogen, heroin, psychotropic, stimulant and other not shown (<50 cases per year).

There are several limitations of this study. ICD-9-CM code limitations, as well as variations in practice across clinical settings, complicate the determination of a "best" definition of NAS for accurately identifying cases caused by maternal substance use. Some studies have included a broader array of codes to capture NAS (eg, 760.7x, noxious influences affecting fetus or newborn via placenta or breast milk).[3,18] For this analysis a more conservative definition was used to improve specificity at the risk of underestimating the true burden of NAS.

The number of NAS-diagnosed newborns lacking a specific substance exposure code, as well the newborns identified with only an opioid exposure code but no NAS code, also may be a product of coding obstacles and practice variations. The latter group may contain missed NAS cases. Further challenges arise when trying to exclude newborns with NAS due to iatrogenic causes. The array of exclusion diagnoses used in this analysis, while informed by previous studies, is not comprehensive.[1,3,4,9] Without additional clinical information, there could be misclassification of newborns with and without NAS due to maternal substance use. Future studies should build upon existing analyses to improve case ascertainment for NAS, including accurate identification of substance exposure and appropriate exclusions for iatrogenic causes to ensure appropriate classification of cases.

The reliance on ICD-9-CM codes captured at time of delivery to identify maternal substance use also may underestimate the use rates. The episode of hospital care at time of delivery is only one snapshot within a longer prenatal course during which substance use may have affected pregnancy. Fear of reporting substance use due to the potential consequences, and the absence of universal substance use screening protocols during delivery hospitalization could result in missed cases. Future work using linked data sets, such as HDD and birth certificate data, and exploration of the clinical record could aid in associating newborn outcomes from specific maternal exposures, provide additional variables of interest (eg, maternal education), and enable more complex regression analysis using continuous variables (eg, birth weight). A better understanding of clinical coding and screening practices also may ensure more comprehensive and consistent surveillance.

Incomplete variables within the dataset, such as missing information for race (15.2%) and ethnicity (19.1%) in newborns, could misrepresent the burden and disproportionate risk of NAS across groups. Missing data is one potential explanation for the discordance in risks observed for NAS and maternal substance use within racial groups. Although black newborns had a decreased risk of NAS compared to white newborns, there was an increased risk of any maternal substance use, and specifically opioid use, in black women compared to white women. Other factors that could affect findings across different demographic groups include disparate screening, reporting, prescribing, or management practices. Previous literature, for example, has shown that providers are less likely to prescribe opioids to some minority groups compared to whites presenting with similar medical problems.[19] Inclusion of birth certificate data in future analyses may help overcome the

Table 3. Maternal Demographic Characteristics and Payer Source for Delivery Hospitalizations With and Without Substance Use in Wisconsin, 2009-2014

	Delivery Hospitalizations Without Substance Use **No. (%)**	Delivery Hospitalizations With Substance Use **No. (%)**	Substance Use Rate Per 1,000 **(95% CI)**	Rate Ratio[a] **(95% CI)**	Delivery Hospitalizations With Opioid Use **No. (%)**	Opioid Use Rate Per 1,000 **(95% CI)**	Rate Ratio[a] **(95% CI)**
Age (years)[b]							
0 to 19	23,835 (6.7)	2,752 (8.1)	103.5 (99.6, 107.4)	Ref	169 (3.8)	6.4 (5.4, 7.4)	Ref.
20 to 29	184,247 (51.9)	22,210 (65.0)	107.6 (106.2, 109.0)	1.0 (1.0, 1.1)	2,719 (61.2)	13.2 (12.7, 13.7)	2.1 (1.8, 2.4)
30 to 39	138,675 (39.1)	8,721 (25.5)	59.2 (58.0, 60.4)	0.6 (0.5, 0.6)	1,477 (33.2)	10.0 (9.5, 10.5)	1.6 (1.3, 1.8)
40 to 55	8,049 (2.3)	498 (1.5)	58.3 (53.2, 63.4)	0.6 (0.5, 0.6)	79 (1.8)	9.2 (7.2, 11.2)	1.5 (1.1, 1.9)
Ethnicity[c]							
Non-Hispanic	309,075 (87.1)	31,935 (93.4)	93.6 (92.6, 94.6)	Ref	4,124 (92.8)	12.1 (11.7, 12.5)	Ref.
Hispanic	32,333 (9.1)	1,050 (3.1)	31.5 (29.6, 33.4)	0.3 (0.3, 0.4)	211 (4.8)	6.3 (5.4, 7.2)	0.5 (0.5, 0.6)
Race[d]							
White	270,777 (76.3)	27,178 (79.5)	91.2 (90.1, 92.3)	Ref	3,476 (78.2)	11.7 (11.3, 12.1)	Ref.
Black	35,934 (10.1)	4,225 (12.4)	105.2 (102.0, 108.4)	1.2 (1.1, 1.2)	558 (12.6)	13.9 (12.7, 15.1)	1.2 (1.1, 1.3)
Asian or Pacific Islander	15,453 (4.4)	421 (1.2)	26.5 (24.0, 29.0)	0.3 (0.3, 0.3)	45 (1.0)	2.8 (2.0, 3.6)	0.2 (0.2, 0.3)
American Indian/ Alaskan Native	3,864 (1.1)	1,066 (3.1)	216.2 (203.2, 229.2)	2.4 (2.2, 2.5)	134 (3.0)	27.2 (22.6, 31.8)	2.3 (2.0, 2.8)
Other	18,249 (5.1)	592 (1.7)	31.4 (28.9, 33.9)	0.3 (0.3, 0.4)	114 (2.6)	6.1 (5.0, 7.2)	0.5 (0.4, 0.6)
Payer							
Private insurance	211,382 (59.6)	8,696 (25.4)	39.5 (38.7, 40.3)	Ref	1,400 (31.5)	6.4 (6.1, 6.7)	Ref
Medicaid	131,440 (37.1)	23,985 (70.2)	154.3 (152.3, 156.3)	3.9 (3.8, 4.0)	2,858 (64.3)	18.4 (17.7, 19.1)	2.9 (2.7, 3.1)
Other	11,988 (3.4)	1,500 (4.4)	111.2 (105.6, 116.8)	2.8 (2.7, 3.0)	186 (4.2)	13.8 (11.8, 15.8)	2.2 (1.9, 2.5)

[a]Rate ratios represent the rate of substance use or opioid use in each group compared to the rate of substance use or opioid use in the reference group.
[b]Missing for 9 women with no substance use (<0.5%) and 9 women with no opioid use (<0.5%).
[c]Missing for 13,401 women with no substance use (3.8%), 1,197 women with substance use (3.5%), and 109 women with opioid use (2.5%).
[d]Missing for 10,533 women with no substance use (3.0%), 700 women with substance use (2.1%), and 117 women with opioid use (2.6%).

gaps in newborn demographic information observed in this study.

Despite these limitations, this study describes the growing burden of NAS and maternal substance use, particularly of opioids, in Wisconsin. The findings, supplemented by a growing body of literature showing the potential negative impacts of NAS and maternal opioid use during and beyond the perinatal period, provide evidence for targeted investments in clinical, public health, and policy initiatives aimed at all levels of prevention and care for mothers and newborns, paying particular attention to those populations with the highest burdens and risks. Early interventions, ideally preventing an opioid-affected pregnancy in the first place, should be top priority.

The ever-growing public health conversation and heightened clinical awareness of NAS and maternal opioid use may help overcome some of the aforementioned challenges of this study through increased diligence in screening, diagnosis, and documentation. Some states have developed universal substance screening procedures for delivering mothers and infants, mandated reporting policies, and statewide real-time surveillance mechanisms to better capture maternal substance use and subsequent newborn impacts.[9,18] Wisconsin has not implemented such strategies, making up-to-date and accurate monitoring more challenging. Conversations between clinical providers, policy decision-makers, public health professionals, and community organizations can lead to improved surveillance approaches, better interventions for substance-using mothers and their children, and prevention strategies that will be essential to ensure the best birth outcomes possible in light of increasing opioid use in Wisconsin and across the nation.

Funding/Support: This study was supported in part by an appointment to the Applied Epidemiology Fellowship Program administered by the Council of State and Territorial Epidemiologists (CSTE) and funded by the Centers for Disease Control and Prevention (CDC) Cooperative Agreement Number 1U38OT000143-02. The Wisconsin Partnership Program, in support of the University of Wisconsin Preventive Medicine Residency Program, provided additional funding.

Financial Disclosures: None declared.

Planners/Reviewers: The planners and reviewers for this journal CME activity have no relevant financial relationships to disclose.

REFERENCES

1. Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. *JAMA.* 2012; 307(18):1934-1940.

2. Association of State and Territorial Health Officials. Neonatal Abstinence Syndrome: How States Can Help Advance the Knowledge Base for Primary Prevention and Best Practices of Care. http://www.astho.org/prevention/nas-neonatal-abstinence-report/. Published 2014. Accessed November 18, 2016.

3. Creanga AA, Sabel JC, Ko JY, et al. Maternal drug use and its effect on neonates: a population-based study in Washington State. *Obstet Gynecol.* 2012;119(5):924-933.

4. Tolia VN, Patrick SW, Bennett MM, et al. Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *N Engl J Med.* 2015;372:2118-2126.

5. Kocherlakota P. Neonatal abstinence syndrome. *Pediatrics*. 2014;134(2):e547-e561.

6. Hamden A. Neonatal Abstinence Syndrome. Medscape. http://emedicine.medscape.com/article/978763-overview. Last updated Nov. 27, 2016. Accessed December 15, 2016.

7. Broussard CS, Rasmussen SA, Reefhuis J, et al; and the National Birth Defects Prevention Study. Maternal treatment with opioid analgesics and risk for birth defects. *Am J Obstet Gynecol.* 2011; 204(4):314,e1-11.

8. Wahlsten VS, Sarman I. Neurobehavioural development of preschool-age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy. *Acta Paediatr*. 2013; 102(5):544-549.

9. Bauer A, Li Y. Neonatal Abstinence Syndrome and Maternal Substance Abuse in Tennessee, 1999-2011. Tennessee Department of Health, Nashville, TN. https://www.tn.gov/assets/entities/health/attachments/Neonatal_Abstinence_Syndrome_and_Maternal_Substance_Abuse_in_Tennessee_1999-2011.pdf. Published 2013. Accessed December 10, 2016.

10. Substance Abuse and Mental Health Services Administration, Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-48, HHS Publication No. (SMA) 14-4863. Rockville, MD: Substance Abuse and Mental Health Services Administration. https://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.pdf. Published September 2014. Accessed December 10, 2016.

11. Silahu HM, Mogos MF, Salinas-Miranda AA, Salemi JL, Whiteman VE. National trends in maternal use of opioid drugs among pregnancy-related hospitalizations in the United States, 1998 to 2009. *Am J Perinatol.* 2015 Feb; 32(3):289-298.

12. Ailes EC, Dawson AL, Lind JN, et al; Centers for Disease Control and Prevention. Opioid prescription claims among women of reproductive age — United States, 2008–2012. *MMWR Morb Mortal Wkly Rep*. 2015;64(2):37-41.

13. Finer LB, Zolna MR. Shifts in intended and unintended pregnancies in the United States, 2001–2008. *Am J Public Health*. 2014;104(Suppl 1):S43-48.

14. Wisconsin State Council on Alcohol and Other Drug Abuse Prevention Committee, Controlled Substances Workgroup. Reducing Wisconsin's Prescription Drug Abuse: A Call to Action. https://scaoda.wisconsin.gov/scfiles/prevspf/FINAL01032012CSWReport.pdf. Published January, 2012. Accessed December 10, 2016.

15. Kuklina EV, Whiteman MK, Hillis SD. An enhanced method for identifying obstetric deliveries: implications for estimating maternal morbidity. *Matern Child Health J*. 2008;12:469-477.

16. Patrick SW, Dudley J, Martin PR, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics*. 2015;135(5):842-850.

17. Massatti R, Falb M, Yors A, Potts L, Beeghly C, Starr S. Neonatal abstinence syndrome and drug use among pregnant women in Ohio, 2004-2011. Columbus, OH: Ohio Department of Mental Health and Addiction Services. http://www.healthy.ohio.gov/~/media/HealthyOhio/ASSETS/Files/injury prevention/NAS Report FINAL.ashx. Published November, 2013. Accessed December 10, 2016.

18. Lind JN, Petersen EE, Lederer PA, et al; Centers for Disease Control and Prevention. Infant and maternal characteristics in neonatal abstinence syndrome—selected hospitals in Florida, 2010–2011. *MMWR Morb Mortal Wkly Rep.* 2015;64(8):213-216.

19. Pletcher MJ, Kertesz SG, Kohn MA, Gonzales R. Trends in opioid prescribing by race/ethnicity for patients seeking care in US emergency departments. *JAMA*. 2008;299(1):70-78

CME

To receive CME credit, complete this quiz and return it to the address listed below. See CME-designated article on pages 287-293.

Quiz: Neonatal Abstinence Syndrome and Maternal Substance Use in Wisconsin, 2009-2014

EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants will be able to:

1. Apply population health principles and management to their practice and health care provision.
2. Identify the potential adverse health conditions related to neonatal abstinence syndrome (NAS) and maternal substance use.

PUBLICATION DATE: December 28, 2016

EXPIRATION DATE: December 28, 2017

QUESTIONS

1. For the study period of 2009–2014, opioids were the second leading substance identified in mothers delivering in the hospital, with the first substance being
   - ❑ Cocaine
   - ❑ Alcohol
   - ❑ Tobacco
   - ❑ Cannabis
2. In which age group was the rate of maternal opioid use highest:
   - ❑ 0 – 39
   - ❑ 20 - 29
   - ❑ ≥ 40
   - ❑ 0 – 19
3. Which subgroups are disproportionately affected by maternal substance abuse resulting in neonatal abstinence syndrome (NAS) for their newborns?
   - ❑ A. American Indian
   - ❑ B. Alaska Native
   - ❑ C. Black
   - ❑ D. White
   - ❑ E. Hispanic
   - ❑ A, B, and D above
   - ❑ A, C, and E above
4. Newborns with NAS usually require medical treatment resulting in prolonged hospital stays. NAS can manifest through a constellation of behavioral and physiological signs and symptoms. Of the symptoms listed below, which one is NOT identified as directly correlated to NAS:
   - ❑ Seizures
   - ❑ Feeding difficulties
   - ❑ Respiratory problems
   - ❑ Jaundice
   - ❑ Prematurity
5. Measuring the rates of maternal substance use in pregnant women presenting for delivery across Wisconsin is complicated by all of the following EXCEPT:
   - ❑ Lack of reporting by the patient
   - ❑ Lack of health insurance coverage
   - ❑ Varying screening practices by providers
   - ❑ Limitations of ICD coding
   - ❑ Different health records systems used across the state
6. Exposure to opioids in utero can cause NAS, but other substances also can cause NAS. Of the following, which has NOT been found to cause NAS:
   - ❑ Cocaine
   - ❑ Benzodiazepines
   - ❑ Antiepileptics
   - ❑ Amphetamines
   - ❑ Cannabis
7. During the study period 2009–2014, which substance, in addition to opioids, showed the greatest increase in use:
   - ❑ Cocaine
   - ❑ Benzodiazepines
   - ❑ Stimulants
   - ❑ Barbiturates
   - ❑ Cannabis

• • •

You may earn CME credit by reading the designated article in this issue and successfully completing the quiz (>75% correct). Return completed quiz to *WMJ* CME, 330 E. Lakeside St, Madison, WI 53715 or fax to 608.442.3802. You must include your name, address, telephone number and e-mail address. You will receive an e-mail from wmj@wismed.org with instructions to complete an online evaluation. Your certificate will be delivered electronically.

The Wisconsin Medical Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The Wisconsin Medical Society designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Access to Primary Care and Subspecialty Care After Positive Cystic Fibrosis Newborn Screening

Katelyn Parker-McGill, MD, MPH; Marjorie Rosenberg, PhD; Philip Farrell, MD, PhD

ABSTRACT

Problem Considered: Accessibility by telephone to cystic fibrosis (CF) centers for a diagnostic sweat test appointment from a parental perspective—which can be stressful—compared to experience in contacting a general pediatrics practice in the same area.

Methods: We called each CF center and affiliate twice, plus a sample of multiphysician general pediatrics practices selected from yellowpages.com after being matched by area and ZIP codes to 50 randomly selected CF centers, including Wisconsin's 2 nationally accredited centers. After alerts to CF centers nationally, we made follow-up calls to randomly selected centers. A call was considered successful if the center or practice provided the time and date of the next available sweat test or well-baby checkup appointment.

Results: In contrast to calls made to general pediatricians' offices, in which 98% were successful and an appointment was available in an average of 8.6 days, only 31% of CF centers and affiliates could be contacted successfully. Although a sweat test appointment was available in 4.9 days on average, delays as long as 26 days were possible. In subsequent follow-up calls, only 40% were successful.

Conclusions: Substantial difficulties and inconsistencies were encountered in accessing CF centers, suggesting that parents often may be challenged in their efforts, while they generally have no difficulty contacting and scheduling an appointment with a general pediatrician. This contrasting experience could be stressful to parents when their baby has a positive screening test. The role of primary care physicians in newborn screening communications is increasingly important, while the role of regional centers needs reconsideration.

• • •

Author Affiliations: Medical College of Wisconsin, Children's Research Institute, Center for Patient Care and Outcomes Research, Milwaukee, Wis (Parker-McGill, Farrell); Departments of Pediatrics and Population Health Sciences, University of Wisconsin School of Medicine and Public Health (UWSMPH), Madison, Wis (Parker-McGill, Farrell); Department of Biostatistics and Medical Informatics, UWSMPH (Rosenberg); Wisconsin School of Business, University of Wisconsin-Madison, Madison, Wis (Rosenberg).

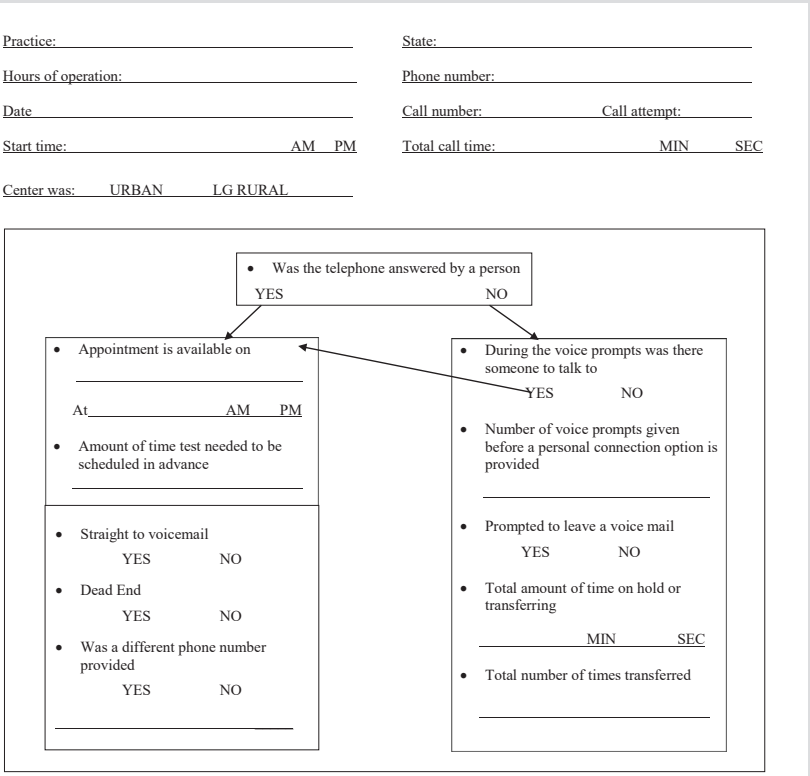
Corresponding Author: Philip M. Farrell, MD, PhD, Depts. of Pediatrics and Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Clinical Sciences Center, 600 Highland Ave, Madison, WI 53792; phone 608.263.8555; e-mail pmfarrell@wisc.edu.

INTRODUCTION

Cystic fibrosis (CF), the most common, life-threatening genetic disease in the Caucasian population,[1] is difficult to diagnose and treat effectively without newborn screening (NBS).[2] After evidence of screening benefits was published,[3,4] and the Centers for Disease Control and Prevention (CDC) recommended this diagnostic strategy,[5] a proliferation of CF NBS programs occurred rapidly and by 2010 the entire United States was screening. It was anticipated by the CDC[5] and CF Foundation[6] that the network of accredited CF centers would facilitate the nationwide implementation of CF NBS programs in partnership with primary care physicians, particularly the follow-up communications and care.[6] Recently published guidelines[7] emphasize the importance of this partnership and excellent, timely communications. On the other hand, previous studies[8] revealed that regional newborn screening programs vary widely in their approaches to communications with parents. In addition, parents have expressed concerns regarding access to a diagnostic sweat test appointment for their newborn.[9] Data indicate that a delay in access can result in psychosocial stress and also has potential adverse consequences for the health of the infant.[10,11] Indeed, it has been observed that "most parents of infants with abnormal NBS results for CF experience a significant amount of distress during their wait for the final diagnostic results."[9,12]

Although access to care by parents for potentially ill infants is obviously crucial, studies are very limited, especially attempts to determine accessibility through telephone calls. No such study could be found in a PubMed search or from the American

Figure. Data Collection Tool for Telephone Survey on Accessibility



Basic data collected and recorded for each call included the provider's name, US state of operation, hours of operation, telephone number, telephone call start and end time, total telephone call time, date of telephone call, urban or large rural status, and the call round. During the telephone call, the following additional information was recorded: if the telephone was answered by a person, language options, if we were prompted to leave a voicemail, the telephone number if an alternative telephone number was provided, if there was someone to talk to during the voice prompts, if new patients were being accepted, if and when (date and time) an appointment was available for a sweat test or well-baby visit, the amount of time needed to schedule the sweat test and if the telephone call ended in a "dead end" (defined as a call that went straight to voicemail, was on hold for more than 10 minutes at one time, was the wrong telephone number, rang for more than 90 seconds without an answer, went to the wrong department within a CF center and could not provide a telephone number or transfer to the correct department, had no proper option in the voice prompts listed at a CF center or affiliate, or ended in a technical or personnel problem). Additional data included the number of voice prompts before a personal connection option is given, total number of voice prompts, total number of times transferred and total amount of time on hold or transferring.

Academy of Pediatrics. Thus, an objective of this project was to design a telephone accessibility study and determine from a parental perspective the accessibility of CF centers compared with nearby general pediatrics practices. The research question, therefore, was how responsive are regional CF centers in the United States to parental inquiry about resources for their infant compared to pediatrician practices. Apparently, this is the first time either clinical setting has been so evaluated nationally, although the topic is considered important.[13]

METHODS

As shown in the Figure, an original telephone survey from a parent's perspective on access was designed and conducted with a script as we attempted to communicate with CF centers/affiliates and then obtain similar data from "matched" general pediatrics practices. The contact information on the 160 certified centers and affiliates was obtained from the CF Foundation for all states and the District of Columbia.

Recognizing that parents would be accustomed to calling primary care physician offices, we carefully selected for comparison during 2012 a total of 50 multiphysician general pediatrics practices using yellowpages.com to identify area and ZIP code groups matched to a 33% random sample of the CF centers. By chance, both of Wisconsin's CF Foundation accredited centers in Madison and Milwaukee were included in the random sample. University and children's hospital practices were excluded in the selection of general pediatricians to ensure that the provider was a distinct, private practice. For Madison and Milwaukee, the immediate, contiguous suburban pediatric practices were eligible for the matching process. When more than one general pediatrics practice was found nearby, the first on the list was selected. Multiphysician general pediatric practices were called once and asked if they were accepting new patients and when the first well-baby checkup appointment was available. The call started with "I'm calling for my daughter who recently had a baby and may be moving into your area."

Each CF center or affiliate in the CF Foundation directory was categorized as urban or rural (by ZIP code), and by size based on the number of patients under the age of 18; they were then categorized as defined by the CF Foundation into large (>65 patients), medium (41-65), small (20-40), or very small (<20). All telephone calls followed the script and were monitored for time using 2 Sportline 240 stopwatches (one used for hold time and other for total call time). Telephone numbers for the first round of calls were from the CF Foundation Directory. After identifying many errors, we utilized telephone numbers for the second round of calls from the online directory of the CF Foundation website (www.cff.org/aboutCF-Foundation/Locations/FindAChapter/). Avoiding holiday weeks such as Thanksgiving, we made 2 calls to each CF center dur-

ing their normal business hours, which were obtained by calling in the evening and obtaining the information from recordings. Additional follow-up calls were conducted about 1 year after this study's initial results were shared with the CF Foundation Centers Committee and pediatric CF centers at large—leading to recommendations/efforts to improve telephone accessibility. Some methods employed were: (1) change in voice prompts, (2) referral of callers to the affiliated children's hospital, (3) more frequent sweat test appointments, and (4) directly answering the phone, ie, reverting to their original telephone communication method. Our repeat assessment method included alphabetizing the list of centers accredited by the CF Foundation and selecting a randomized subset of half of the CF centers that were not successful in the initial calls (N=42). Then, during 2015-2016, a third set of calls was made for additional assessment using an updated resource from the CF Foundation website (www.cff.org/aboutCFFoundation/Locations/FindACareCenter/).

The main outcome variable was to ascertain the earliest time and date that an appointment could be scheduled. Basic data collected and recorded for each call included the responses, response times, transfers and appointment availability. Additional data included the number of voice prompts before a personal connection option is given, total number of voice prompts, total number of times transferred, and total amount of time on hold or transferring. Call outcomes resulted in 3 categories: successful, partially successful, and unsuccessful. A call was deemed successful when both a time and date for the next available appointment were readily available, partially successful if a sweat test date and time were provided during only one of the 2 telephone calls, and unsuccessful if a time/date was not obtained.

Our Institutional Review Board (IRB) determined this study qualified for exemption under category 45 CFR 46.101(b) (2) and did not require informed consent. Members of the IRB contributed to the design and script.

Table 1. Provider Characteristics[a] by Mean Outcome

Provider Access to Care Outcomes	Successful[b] No. (%)	Partially Successful No. (%)	Unsuccessful No. (%)
Designation			
Centers (n=110)	33 (30)	42 (38)	35 (32)
Affiliates (n=50)	16 (32)	14 (28)	20 (40)
Centers + Affiliates (n=160)	49 (31)	56 (34)	55 (34)
Location			
Urban (n=156)	45 (29)	56 (36)	55 (35)
Large rural (n=4)	4 (100)	0 (0)	0 (0)
Size			
Large, >65 patients (n=87)	29 (33)	28 (32)	30 (35)
Medium, 41-65 patients (n=32)	11 (34)	13 (41)	8 (25)
Small, 20-40 patients (n=28)	4 (14)	11 (39)	13 (47)
Very small, <20 patients (n=13)	5 (38)	4 (31)	4 (31)

[a]Per Cystic Fibrosis Foundation definitions.
[b]All percentages were calculated across rows and within each characteristic.

Table 2. Comparisons of Cystic Fibrosis (CF) Provider and General Pediatrics Practice Telephone Call Outcomes

	CF Centers	CF Affiliates	Pediatric Practices
Successfully provided time and date of next appointment [no. (%)]	33 (30%)	16 (32%)	49 (98%)
Answered by a person[a] [no. (%)]	33.5 (30%)	19.5 (39%)	37 (74%)
Mean total call time (sec)	172	145	124
Range of mean total call time (sec)	38–527	18–699	48–551
Mean hold time (sec)	119	97	144
Range of mean hold time (sec)	0–449	4–640	27–520
Mean time to first appointment (days)	5	5	8.6
Range of mean time to first appointment (days)	1–18	1–26	1–49

Abbreviation: sec, seconds.
[a]The number of providers who are included in this analysis are the summed average of all calls that had call time.

RESULTS

Our primary objective of this survey was accomplished, namely to determine the accessibility by telephone of an appointment for a newborn infant. As shown in Table 1, we found that only 31% (49/160) of the CF centers and affiliates were successful on both rounds of calls, while 34% (55/160) of the CF centers and affiliates were categorized as completely unsuccessful. Although there were a variety of reasons for a lack of success, the most common explanation was an unanswered call. We found that 54% of calls with a "dead end" outcome resulted from the telephone call going straight to voicemail or ending in voicemail. We also found that, on average, when the telephone was answered by a CF center/affiliate, there was an average of 3.8 voice prompts or messages. In contrast, 98% of the calls to general pediatricians' offices were successful and transfer to voicemail occurred only once (Table 2). On average, calls were answered by a person in 22 seconds and appointments made in 8.6 days within 2 minutes and 4 seconds. Eleven of the 50 multiphysician general pediatric providers had one voice prompt and the remaining had zero. Because of the successful matching and very high success rate, we did not repeat these calls or expand the sample.

When a call to a CF center/affiliate was successful, the average total time spent on the telephone was 158 seconds and the time on hold was 106 seconds. Similar results were found with the general pediatrics practices, ie, 124 and 144 seconds, respectively. Table 1 also lists some characteristics for the CF centers and affiliates. These results revealed that there were no significant difference between the centers/affiliates in terms of success rate. CF centers and affiliates also were analyzed by the number of patients under age 18 at their facility. In this analysis, the data suggest

that the small CF centers/affiliates caring for 20 to 40 patients might be less accessible than the others. The data also were analyzed by geographical location and revealed no regional trends (data not shown). From the subset list of 42 CF centers called in the follow-up calls, we found only 40% success in being able to reach the CF scheduler/coordinator and being provided both the date and time of the next available sweat test. Thus, there was no significant improvement compared with our initial experiences. Similar results were found on the third set of calls to CF centers.

The Wisconsin results were typical of our national findings. Specifically, the first call to 1 center was partially successful while the other was unsuccessful. However, on the second call, neither was successful but led to dead-end outcomes as described in the Figure legend. On the other hand, the calls to the matched general pediatricians' offices were all successful.

DISCUSSION

Limited research has been done on timely communications and accessibility for newborns in pediatric practices. We designed/performed an innovative, telephone-based study and found that CF centers have poor access, while nearby general pediatric practices were almost invariably accessible. Two widely accepted definitions of access to care include the Institute of Medicine's—namely "the timely use of personal health services to achieve the best health outcomes"[14]—and the Agency for Healthcare Research and Quality's statement: "Assessments by patients of how easily they are able to gain access to health care."[15] Because parents of newborn infants obviously need to contact physicians on an urgent basis for primary care and sometimes for subspecialist care, we designed this original study from a parental perspective to determine accessibility for either a well-baby visit or for follow-up of a positive NBS test. As emphasized in the pivotal CDC report recommending universal NBS, "The net balance of benefits and risks is contingent on how newborn screening for CF is implemented."[9] Because some of the risks are associated with delays occurring after a positive screening test, we assumed that an important element in the follow-up component would be access. If a delay in access occurs, parental psychological stress becomes an important concern whenever parents face a possible CF diagnosis.[9,10,16] Studies have revealed, "Most parents experienced strong emotional responses to the news of a positive IRT (immunoreactive trypsinogen) test, including anxiety, shock, denial, and anger. Parents also reported heightened vigilance during the typical delay between being informed of a positive IRT results and diagnostic sweat test."[16] These negative experiences are part of the risks of NBS.[5,17]

Because of such risks, it is important that parents have adequate access and are satisfied with their communications. However, in this study, we found that 34% of all CF centers and affiliates in the United States were completely inaccessible by telephone and that only 31% were accessible on both of our attempts. These results show that the majority of such centers cannot be readily contacted and suggest that parental accessibility is a barrier to care. The question can be raised if other kinds of specialty centers would be similarly difficult to contact, but this has not been studied. We considered this as an adjunct study but found that it was difficult to identify a high-performing pediatric specialty with regard to communication and, moreover, this ancillary study would be challenging to design without a published network of centers engaged in NBS. On the other hand, contacting general pediatricians' offices nationwide for an appointment was found to be quick and generally successful with regard to an appointment soon after the call.

According to Best Practices, LLC,[18] telephone call centers on average have a 4% call abandonment rate, and rates that reach 10% or higher should be reviewed for quality improvement. Likewise, it was noted that the majority of benchmark companies improve their center processes based on customer needs.[18] Consequently, the CF Foundation Centers Committee reviewed our results and the pediatric centers were notified about this issue and the need for better communication and quality improvement.[19] Suggestions were made as described previously. The aim of our additional follow-up calls was to determine if these efforts had any impact. Because our data revealed that only 40% of reassessed CF centers were accessible during their second round of calls, and indeed some were less accessible, it is clear further efforts are needed. Recognizing that this may be the case and its responsibility to provide parents with information on the screening and diagnosis of infants, as well as the nature of the disease, the CF Foundation has created the first parent website on NBS (http://www.cff.org/AboutCF/Testing/NewbornScreening/). Although its impact remains to be determined, initial usage has been very impressive, with an average of more than 1955 and 2658 "hits" per month during 2011 and 2012, respectively. The website includes a section "For Health Care Providers" that received 150 to 200 unique views per month. (Data provided by Leslie Hazle, RN, of the CF Foundation by verbal and follow-up e-mail communications during 2015.)

Studies show that "convenient accessibility was the most important factor for the initial choice of primary care doctors by the general public."[20] Our evaluation revealed that general pediatric practices do show "convenient accessibility" during random assessment nationwide. In view of the limited accessibility of the nation's CF centers, however, it must be concluded that primary care providers, especially readily accessible general pediatricians, and informative websites can assume increasingly important roles in communication and facilitation of follow-up procedures after newborn screening and other genetic disorders.

CONCLUSION

Substantial difficulties and inconsistencies were encountered in parental access for scheduling a follow-up appointment with a CF center, indicating that parents often may be challenged in their efforts. On the other hand, we conclude that they generally have no difficulty contacting and scheduling an appointment with a general pediatric practice. This contrasting experience could be a source of stress to parents, especially when their baby has a positive NBS test.[9] However, there are methods that CF centers could employ to improve their accessibility by telephone such as triaging calls to nurse specialists or responsive children's hospitals. From a broader perspective, our results reinforce how responsive and helpful pediatricians and family physicians can be to their patients and families. In addition, this study complements our previous research and emphasizes the need for continued quality improvement in NBS. One aspect of this should be reconsideration of the role of regional centers in NBS follow-up activities if their accessibility is limited.

Acknowledgements: We thank Anita Laxova for her expert assistance in the organization of this study, especially with IRB communication, and Professor Patrick Remington, MD, MPH, for his guidance on aspects of evaluating heath care accessibility. We also appreciate the advice of the CFF, especially Bruce C. Marshall, MD, vice president of clinical affairs, US Cystic Fibrosis Foundation; and our communications with the American Academy of Pediatrics, especially Dr V. Fan Tait, MD, FAAP, associate executive director, Department of Community and Specialty Pediatrics, who recommended that we proceed with this study.

Funding/Support: This research was supported in part through National Institutes of Health grant DK 34108 to Dr Farrell as Principal Investigator.

REFERENCES

1. Kosorok MR, Wei WH, Farrell PM. The incidence of cystic fibrosis. *Stat Med.* 1996;15(5):449-462.

2. Balfour-Lynn I. Newborn screening for cystic fibrosis: evidence for benefit. *Arch Dis Child*. 2008;93(1):7-10.

3. Farrell PM, Kosorok MR, Rock MJ, et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. *Pediatrics*. 2001;107:1-13.

4. Farrell PM, Aronson RA, Hoffman G, Laessig RH. Newborn screening for cystic fibrosis in Wisconsin: first application of population-based molecular genetics testing. *Wis Med J*. 1994;93(8):415-421.

5. Grosse SD, Boyle CA, Botkin JR, et al. Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. *MMWR Morb Mortal Wkly Rep*. 2004;53(RR-13):1–36.

6. Campbell PW, White TB. Newborn screening for cystic fibrosis: an opportunity to Improve care and outcomes. *J Pediatr*. 2005;147(suppl 3):S2-S5.

7. Borowitz D, Robinson KA, Rosenfeld M, et al; and Cystic Fibrosis Foundation. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr*. 2009;155(suppl 6):S73-S93.

8. Farrell M, Certain L, Farrell P. Genetic counseling and risk communication services by newborn screening programs. *Arch Pediatr Adolesc Med*. 2001;155(2):120-126.

9. Tluczek A, Koscik R, Farrell P, Rock M. Psychosocial risk associated with newborn screening for cystic fibrosis: parents' experience while awaiting the sweat-test appointment. *Pediatrics*. 2005;115(6):1692-1703.

10. Sims EJ, Clark A, McCormick J, Mehta G, Connett G, Mehta A; United Kingdom Cystic Fibrosis Database Steering Committee. Cystic fibrosis diagnosed after 2 months of age leads to worse outcomes and requires more therapy. *Pediatrics*. 2007;119(1):19-28.

11. Farrell, PM. The meaning of "early" diagnosis in a new era of cystic fibrosis care. *Pediatrics*. 2007;119(1):156-157.

12. Tluczek, A, Mischler, EH, Farrell, PM, et al. Parents' knowledge of neonatal screening and response to false-positive cystic fibrosis testing. *J Dev Behav Pediatr*. 1992;13(3):181-186.

13. Feinberg R, Kim I, Leigh H. Operational determinants of caller satisfaction in the call center. *Int J Service Industry Manag*. 2000;11(2):131-141.

14. Millman M, ed. Access to health care in America. Institute of Medicine, Committee on Monitoring Access to Personal Health Care Services. Washington, DC: National Academy Press; 1993.

15. National Healthcare Disparities Report. Rockville, MD: Agency for Healthcare Research and Quality, US Department of Health and Human Services; 2011. AHRQ Publication No. 11-0005. https://archive.ahrq.gov/research/findings/nhqrdr/nhdr10/Chap9.html. Accessed December 10, 2016

16. Tluczek A, Koscik RL, Modaff P, et al. Newborn screening for cystic fibrosis: parents' preferences regarding counseling at the time of infants' sweat test. *J Genet Couns*. 2006;15(4):277-291.

17. Baroni MA, Anderson YE, Mischler E. Cystic fibrosis newborn screening: impact of early screening results on parenting stress. *Pediatr Nurs*. 1997;23(2):143-151.

18. Best Practices, LLC. *Managing World-Class Call Centers: Site Visit Findings*. Best Practices, LLC Benchmark Report; 2004.

19. McPhail GL, Weiland J, Acton JD, et al. Improving evidence-based care in cystic fibrosis through quality improvement. *Arch Pediatr Adolesc Med*. 2010;164(10):957-960.

20. Wun YT, Lam TP, Lam KF, Goldberg D, Li DK, Yip KC. How do patients choose their doctors for primary care in a free market? *J Eval Clin Pract*. 2010;16(6):1215-1220.

Effectiveness of a Clinic-Based Early Literacy Program in Changing Parent-Child Early Literacy Habits

Jonathan Fricke, MD, MPH; Dipesh Navsaria, MD, MPH, MSLIS; Karin Mahony, MEd, MSW

ABSTRACT

Background: Reach Out and Read (ROR) improves children's development and kindergarten readiness by encouraging parents to routinely share books with their children. Primary care providers give age-appropriate books and anticipatory guidance on reading at each well-child visit. This study evaluated parent attitudes and behaviors of early literacy related to ROR participation in Wisconsin clinics.

Methods: A survey of early literacy attitudes and behaviors was administered to parents of children ages 6 months to 5 years in 36 Wisconsin clinics. Ten clinics were established ROR sites (intervention group) and 26 clinics had applied to become ROR programs but had not yet initiated the program (control group).

Results: Parents at clinics with ROR programs were more likely to read with a child under the age of 6 months (OR=1.58, 95% CI, 1.05-2.38). Other literacy metrics trended toward improvement but none reached statistical significance. Paradoxically, the odds of parents reporting reading as a bedtime habit were decreased among those who participated in ROR.

Conclusions: Our study finds mixed support of the effectiveness of ROR outside of academic settings. The apparent discrepancy between these results and those from national studies on ROR may be related to differences in respondent demographics and educational attainment or differences in program implementation and fidelity. We believe that the results will become clearer with future study as clinics are prospectively evaluated over time rather than being compared to non-ROR clinics in a cross-sectional snapshot.

BACKGROUND

Reach Out and Read (ROR) is a national clinic-based early literacy program that provides anticipatory guidance on the importance of reading aloud, targeting children from age 6 months to 5 years old. At each health supervision visit, a child receives a new book, and age-appropriate reading techniques are briefly taught to the parents.[1] ROR is a widespread, evidence-based intervention with programs in all 50 states and efficacy demonstrated in over a dozen peer-reviewed journal articles.[1-10] The American Academy of Pediatrics recently recommended that literacy promotion should be a routine part of every well-child visit.[11]

Several factors influence reading habits at home. Nationally, wealthy families are nearly twice as likely to read to children daily as families below the poverty line.[12] In Wisconsin, 60% of parents with more than a high school education report reading to their children every day, compared with the nationwide average of 56%. However, only 38% of Wisconsin parents with a high school education or less report the same. There are also significant racial disparities in reading habits. Sixty-three percent of white families in Wisconsin report reading every day, but only 34% of African American and 40% of Hispanic families report the same.[12] Ultimately, more than 1 in 3 children in Wisconsin starts kindergarten without the language skills they need to learn to read.[13]

Parents who participate in ROR are up to 4 times more likely to read aloud to their children, and children who participate have higher vocabulary scores.[2,6-9] These effects are most pronounced among nonwhite and less educated families.[2-6] The largest study, a 19-center study from 10 states (not including Wisconsin) showed parents to be approximately 1.5 times more likely to read aloud at bedtime, read at least 3 times per week, have picture books in the home, and consider reading aloud to be a favorite activity.[6]

Reach Out and Read Wisconsin was organized in 2010 with 55 participating clinics and has now expanded to more than 160 sites (Figure).[13] In 2014, ROR reached 13% of Wisconsin children, including 18% of those who live at or below 200% of the

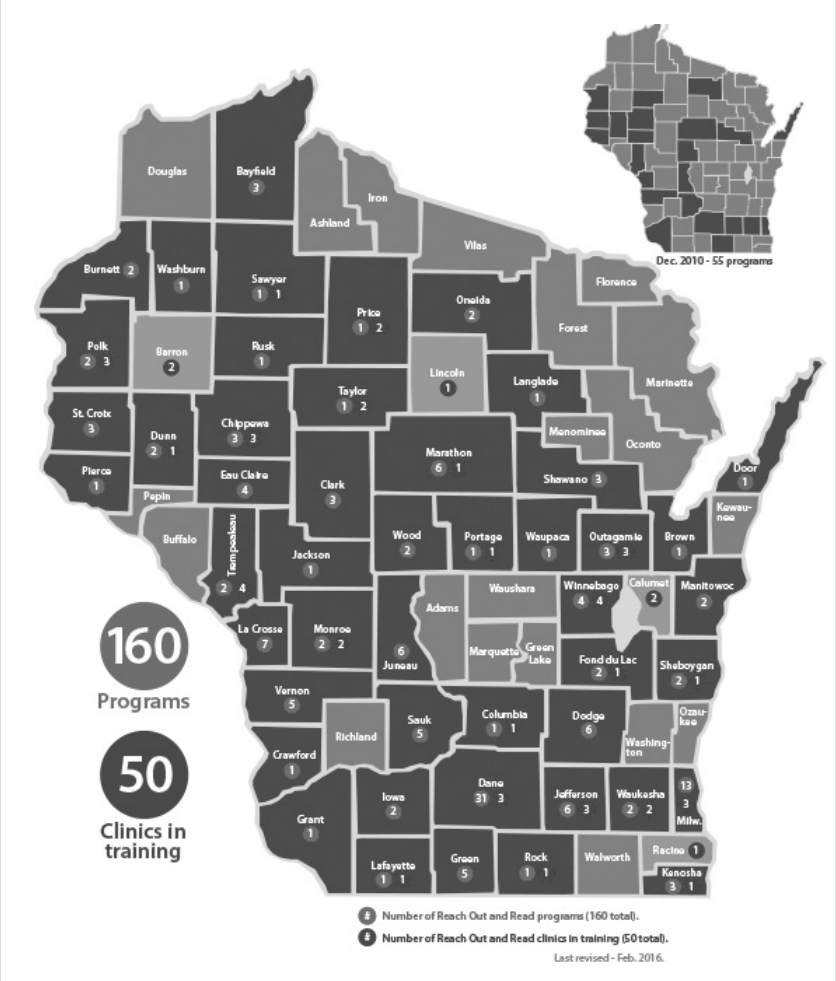
• • •

Author Affiliations: Department of Family Medicine, University of North Carolina School of Medicine, Chapel Hill, NC (Fricke), University of Wisconsin School of Medicine and Public Health, Madison, Wis (Navsaria), Reach Out and Read Wisconsin, West Allis, Wis (Mahony).

Corresponding Author: Jonathan Fricke, MD, MPH, Resident Physician, Department of Family Medicine, University of North Carolina School of Medicine, Chapel Hill, NC; phone 608.467.0891; e-mail jonathan.fricke@unchealth.unc.edu.

Federal Poverty Level.[13] To date, there have been no studies published that evaluate Reach Out and Read in Wisconsin. Here we present preliminary findings from a survey evaluating changes in parental early literacy attitudes and behaviors associated with ROR participation.

Figure. Reach Out and Read Wisconsin Programs



METHODS

Reading habits of families at 36 clinics throughout Wisconsin were compared utilizing a cross-sectional survey. Methods were adapted from an earlier national study of ROR effectiveness by Needlman et al.[6] The intervention group consisted of 10 clinics with current ROR programs, while the control group was comprised of 26 clinics applying to become ROR programs. Clinics in the application process had committed to implementing ROR but had not yet trained their providers in the program model and were not currently providing books or routine anticipatory guidance on reading at well-child visits. All 10 intervention clinics were participants in a grant and were asked to participate in this study as part of the evaluation process of that grant.

Enrollment was conducted by the staff of each clinic. At check-in, parents or guardians (hereafter referred to collectively as parents) of children ages 6 months through 5 years were asked to participate in the survey. To best capture the natural conditions at a clinic, parents in both groups were asked to complete surveys regardless of exposure to ROR. Surveys were available in English, Spanish, and Hmong. Clinics were asked to distribute surveys for 1 month or until they had collected a total of 50 completed surveys, whichever came first. No potentially sensitive or intrusive questions were included on the survey, and subjects were reminded to not include their names or other identifying information on the survey. A waiver of full Institutional Review Board (IRB) approval was obtained via the University of Wisconsin-Madison.

Data were collected by a 1-page, 2-sided paper survey given to parents at patient registration and collected after the clinic visit. Parents were instructed to complete the survey while waiting to be roomed. Surveys included demographic information and 6 core questions based on those used by Needlman et al.[6] The first 3 questions were scored as "1" if the respondent mentioned "reading" or "books" and "0" if the respondent did not. The second 3 questions were based on the StimQ, a 3-question questionnaire that has been validated for internal consistency, test-retest reliability, criterion-related validity, and predictive validity in low-income urban Hispanic/Latino and African American families.[14] Days reading per week was dichotomized as <3 versus ≥3 days per week, and number of books in the home was dichotomized as <10 versus ≥10 days per week.

Control and intervention clinics were compared with univariate analysis followed by multivariate analysis to assess the difference after adjusting for child gender, race/ethnicity (white vs nonwhite), home language (English vs non-English), urban/rural, and parental education level. For binary outcomes, logistic regression model with random effect was fitted using SAS PROC GLIMMIX. Odds ratio, 95% confidence interval, and *P*-value were reported. For continuous outcomes, mixed effect model was fitted using SAS PROC MIXED. LSEANS, 95% CI, and *P*-value were reported. The analysis was conducted using SAS 9.4. (SAS Institute, Cary, North Carolina).

A secondary analysis was carried out after excluding the 11

Table 1. Descriptive Statistics of Survey Respondents and Their Children

	Control	Intervention	Wisconsin[15-17]
Relationship to Child			
Father	13.2%	13.2%	--
Mother	85.6%	85.1%	--
Grandparent	1.0%	0.8%	--
Nonrelative caregiver	0.1%	0.1%	--
Respondents With College Education or Higher	54.5%	59.9%	37.8%[a]
Average Age of Child (Months)	25.3	24.1	--
Percent Female (Child)	47.3%	48.3%	--
Race or Ethnicity of Child			
White	84.5%	74.2%	69.7%[b]
Black or African American	2.2%	4.0%	8.9%
Hispanic or Latino	3.3%	2.3%	12.1%
American Indian or Alaska Native	0.9%	5.9%	1.2%
Asian	4.3%	6.0%	3.7%
Native Hawaiian or Pacific Islander	0.0%	0.3%	<0.5%
Multiple races	4.8%	7.4%	4.3%
Primary Language Spoken in the Home			
English only	91.6%	93.8%	88.5%[c]
Speak Spanish	3.7%	1.4%	6.8%
Speak Hmong	1.4%	2.5%	--
Other	3.1%	2.3%	4.6%

[a]2014 American Community Survey (ACS) 5-year estimate of Wisconsin residents. >25 years old with a college degree or higher, regardless of parenthood status. ACS Table S1501.
[b]2014 estimate of Wisconsin children ages 0-4.
[c]2013 ACS 3-year estimate of Wisconsin children ages 5-17. The ACS does not assess primary language spoken for children ages 0-4. Home language is reported as "English only," "Spanish," and "all other languages." ACS Table C16007.

Table 2. Results of Univariate Analysis

Outcome	Odds Ratio (Established vs New)	95% CI	*P*-value
Reading as favorite thing to do	0.95	0.72, 1.26	0.7308
Reading to prepare for sleep	0.71	0.53, 0.94	**0.0183**
Reading to prepare for kindergarten	1.29	0.97, 1.72	0.0824
Appropriate to start reading at <6 mo.	1.30	0.90, 1.88	0.1569
More than 5 books at home	1.03	0.60, 1.78	0.9016
More than 10 books at home	1.03	0.69, 1.52	0.8956
Read 3 or more days a week	1.53	0.84, 2.79	0.1611
Read 5 or more days a week	0.96	0.71, 1.30	0.7813

Statistically significant results are bolded.

clinics in Dane County. Madison, the state capital and home to the University of Wisconsin-Madison, is a community with high socioeconomic and education levels. Additionally, in the years leading up to this study, there had been significant publicity in the city related to early literacy and ROR. For these reasons, it was determined to be possible that parents at Dane County clinics may be more familiar with the concepts of early education and early literacy, thereby affecting the survey results.

RESULTS

Overall, 1,025 surveys were collected from 36 clinics (an average of 28.5 surveys per clinic, min=5, max=51). The control group consisted of 670 surveys from 26 clinics in the process of implementing ROR programs. The intervention group contained 355 surveys from 10 clinics with programs established for more than a year.

The control group had a higher proportion of clinics located in Dane County (38.5% vs 10.0%), as well as a higher percentage of clinics in rural counties (39.0% vs 25.6%). Respondents in the control and intervention groups were similarly likely to have completed college and report visiting the library. In both groups, the majority of respondents were mothers (Table 1).

The average age and gender of children was similar for both control and intervention groups. The control group had a higher proportion of white children compared with the intervention group (84.5% and 74.2%). English was the language most commonly spoken at home, with Spanish (3.7% and 1.4%) and Hmong (1.4% and 2.5%) being the most common other languages spoken (Table 1).

After univariate analysis, the only statistically significant difference was that parents participating in ROR were paradoxically less likely to report reading as a part of a bedtime routine (OR=0.71) (Table 2). Parents also were more likely to see reading together as helping to prepare their children for kindergarten, although this neared, but did not reach, statistical significance (OR=1.29, *P*=0.082).

After multivariate analysis, parents were more likely to list an age of ≤6 months as an "appropriate age to begin reading" (OR=1.58) (Table 3). Increases in other metrics trended toward, but did not reach, statistical significance. After excluding Dane County clinics and repeating multivariate analysis, the likelihood of parents listing an age of ≤6 months as "appropriate age to begin reading" increased (OR=1.77).

Multivariate analysis also showed that parent education, ethnicity, and home language were associated with home reading habits. Parents with a college education or higher were more likely to read as a part of the bedtime routine, mention reading as a step to prepare children for kindergarten, and list an age of ≤6 months as "appropriate age to begin reading." These parents had more books in the home and read more often than those with less than a college education (Table 3). Similar correlations with ethnicity and home language were noted, with whites and English-speakers being more likely to report proliteracy habits at home.

DISCUSSION

At present, there are well over a dozen peer-reviewed studies demonstrating the efficacy of ROR. This study contributes by assess-

Table 3. Results of Multivariate Analysis

Outcome	Variable	All Clinics				Excluding Dane County Clinics			
		Odds Ratio	95% CI		*P*-value	Odds Ratio	95% CI		*P*-value
Reading as Favorite Thing to Do	Established vs new	1.01	0.76	1.35	0.9332	1.10	0.76	1.58	0.5984
	Female vs male	1.12	0.85	1.47	0.4180	1.06	0.76	1.49	0.7127
	White vs non-white	1.31	0.87	1.97	0.1943	1.29	0.77	2.16	0.3120
	English vs non-English	1.25	0.67	2.34	0.4601	1.28	0.57	2.86	0.5313
	Rural vs non-rural	1.09	0.81	1.48	0.5441	1.17	0.81	1.68	0.3776
	High school vs college	1.25	1.00	1.43	0.0512	1.47	1.04	2.06	**0.0305**
Reading to Prepare for Sleep	Established vs new	0.77	0.57	1.03	0.0783	0.84	0.58	1.22	0.3350
	Female vs male	1.14	0.86	1.52	0.3621	1.17	0.83	1.65	0.3535
	White vs non-white	1.45	0.95	2.19	0.0802	1.25	0.75	2.09	0.3726
	English vs non-English	1.47	0.79	2.74	0.2179	1.90	0.86	4.21	0.1054
	Rural vs non-rural	1.16	0.85	1.59	0.3415	1.34	0.92	1.95	0.1144
	High school vs college	1.47	1.28	1.60	**0.0002**	1.82	1.28	2.58	**0.0022**
Reading to Prepare for Kindegarten	Established vs new	1.33	0.97	1.81	0.0733	1.43	0.98	2.08	0.0645
	Female vs male	0.85	0.64	1.14	0.2758	0.96	0.68	1.36	0.8272
	White vs non-white	1.36	0.89	2.07	0.1453	1.25	0.74	2.10	0.3893
	English vs non-English	1.39	0.75	2.59	0.2840	1.35	0.61	2.97	0.4355
	Rural vs non-rural	0.85	0.62	1.16	0.2958	0.94	0.65	1.36	0.7251
	High school vs college	1.49	1.32	1.62	**<.0001**	1.68	1.18	2.39	**0.0064**
<6 Months Appropriate to Start Reading	Established vs new	1.58	1.05	2.38	0.0285	1.77	1.09	2.88	0.0237
	Female vs male	0.87	0.60	1.26	0.4521	0.81	0.52	1.26	0.3321
	White vs non-white	2.20	1.35	3.59	**0.0026**	2.57	1.43	4.61	**0.0032**
	English vs non-English	1.55	0.78	3.08	0.2014	1.60	0.69	3.69	0.2530
	Rural vs non-rural	1.03	0.69	1.54	0.8701	1.11	0.69	1.77	0.6570
	High school vs college	1.54	1.32	1.68	**0.0003**	1.80	1.14	2.83	**0.0146**
More Than 5 Books at Home	Established vs new	1.21	0.66	2.20	0.5197	0.98	0.48	2.01	0.9544
	Female vs male	0.97	0.55	1.71	0.9145	1.04	0.54	2.02	0.9018
	White vs non-white	1.99	0.98	4.05	0.0579	1.99	0.84	4.70	0.1107
	English vs non-English	6.16	2.65	14.32	**0.0002**	5.47	2.00	14.96	**0.0024**
	Rural vs. non-rural	1.53	0.81	2.87	0.1782	1.38	0.68	2.80	0.3490
	High school vs college	1.85	1.70	1.92	**<.0001**	5.30	2.25	12.44	0.0006
More Than 10 Books at Home	Established vs new	1.14	0.73	1.78	0.5588	1.28	0.75	2.18	0.3425
	Female vs male	1.21	0.79	1.85	0.3739	1.27	0.78	2.08	0.3223
	White vs non-white	2.90	1.73	4.88	**0.0002**	2.94	1.59	5.43	**0.0016**
	English vs non-English	4.23	2.11	8.49	**0.0003**	3.32	1.43	7.70	0.0080
	Rural vs non-rural	0.68	0.43	1.05	0.0786	0.78	0.46	1.32	0.3370
	High school vs college	1.46	1.02	1.70	**0.0447**	2.63	1.55	4.44	**0.0011**
Read 3 or More Days a Week	Established vs new	1.47	0.77	2.80	0.2296	1.11	0.50	2.48	0.7858
	Female vs male	1.12	0.62	2.02	0.6940	1.14	0.55	2.36	0.7088
	White vs non-white	1.05	0.44	2.46	0.9160	0.77	0.24	2.44	0.6444
	English vs non-English	5.17	2.01	13.27	**0.0015**	9.36	2.76	31.71	**0.0012**
	Rural vs non-rural	1.37	0.71	2.66	0.3362	1.28	0.58	2.82	0.5207
	High school vs college	1.46	1.02	1.70	**0.0447**	1.70	0.79	3.64	0.1651
Read 5 or More Days a Week	Established vs new	1.05	0.75	1.47	0.7514	1.24	0.82	1.86	0.2881
	Female vs male	0.84	0.61	1.15	0.2657	0.93	0.64	1.36	0.7069
	White vs non-white	2.19	1.43	3.35	**0.0008**	2.15	1.27	3.63	**0.0065**
	English vs non-English	2.23	1.18	4.18	**0.0151**	2.85	1.25	6.50	**0.0157**
	Rural vs non-rural	0.87	0.62	1.21	0.3883	1.05	0.70	1.57	0.8153
	High school vs college	1.48	1.29	1.63	**0.0002**	1.73	1.18	2.54	**0.0070**

The first group, "All clinics" is comparison of 1,025 surveys from 26 control and 10 intervention clinics.
The second group, "Excluding Dane County Clinics" is 705 surveys from 25 clinics after excluding all control and intervention clinics from Dane County.
Statistically significant results are bolded.

ing ROR outside academic clinical settings and in Wisconsin specifically. The results offer support of previous studies, showing parents participating in ROR to be more likely to display healthy attitudes and behaviors related to early literacy. Parents participating in ROR were more likely to read with their kids before age 6 months compared with parents who had not participated in ROR (OR=1.58), and these results were strengthened after exclusion of Dane County clinics (OR=1.77). Parents also were more likely to see reading as preparing their children for kindergarten, read more often with their children, and have more books in the home, although these increases did not reach statistical significance. Paradoxically, the odds of parents reporting reading as a bedtime habit were decreased among those who participated in ROR.

The benefits of ROR were not demonstrated as consistently or dramatically as in previous studies. It is likely that comparing 2 different groups of clinics introduced confounding variables. This study is an initial report from the first stage of a larger study that will longitudinally study parent survey responses before and after implementation of ROR programs in clinics. This prospective model will minimize the challenges posed by comparing 2 different groups of clinics.

Of note, the percentage of respondents with college education or higher (54.5% and 59.9% of control and interventional groups, respectively) is notably higher than the Wisconsin state average of 37.8%.[15] As previous studies have noted, ROR has its most dramatic impact among families with lower educational attainment. It is possible that our sample captured a disproportionately high percentage of Wisconsin.

Approximately 80% of respondents in this study were white, compared to 72% of the US population and 86% of the general population Wisconsin.[17] Needlman et al found impact of ROR among African-Americans and Latinos, but not whites, participating in ROR.[6] The small number of nonwhite participants in our surveys limits sub-analysis based on race. However, given the large percentage of whites in our population relative to the study by Needlman, results from this study would be expected to be less pronounced than those results.

It is likely that control group clinics had not implemented ROR programs until now because the need was not as great or apparent as it was for early adopters of the program, many of which were community health centers or located in poorer communities.

Despite being a statewide survey, the sample was not comprehensive and only included a small portion of the more than 150 ROR programs in Wisconsin. The rate of parents declining to participate is unknown. It is likely that the written format of the survey discouraged or prevented some parents from participating — particularly those with low literacy skills.

This study raises the question of whether paper surveys are sufficient and effective tools in evaluation of the impact of ROR in nonacademic settings. Although imperfect, the paper survey offers significant convenience and cost savings when compared with use of trained interviewers; however, their validity needs to be evaluated.

CONCLUSION

Reach Out and Read has been shown to be successful on the national level in changing parent attitudes and behaviors toward reading with children. The results of this preliminary report from an ongoing study offer some support of previous studies, demonstrating that parents participating in ROR are more likely to read with their children before they are 6 months old. Other literacy metrics trended toward improvement but did not reach statistical significance. We believe that the results will become clearer when clinics are prospectively evaluated over time rather than being compared to other clinics in a cross-sectional snapshot. Future studies of ROR programs in nonacademic settings should pay particular attention to the fidelity of programs to the ROR program model. Additionally, studies should also focus on assessing the effects of parental education, language spoken in the home, and ethnicity on home literacy habits.

Funding/Support: None declared.

Financial Disclosures: None declared.

REFERENCES

1. Klass P, Needlman R, Zuckerman B. Reach Out and Read Program Manual. 2nd ed. Boston, MA: Reach Out and Read National Center, Boston Medical Center; 1999.

2. Needlman R, Fried LE, Morley DS, Taylor S, Zuckerman B. Clinic-based intervention to promote literacy. A pilot study. *Am J Dis Child*. 1991;145(8):881-884.

3. Klass P, Dreyer BP, Mendelsohn AL. Reach out and read: literacy promotion in pediatric primary care. *Adv Pediatr*. 2009;56:11-27.

4. Sanders LM, Gershon TD, Huffman LC, Mendoza FS. Prescribing books for immigrant children: a pilot study to promote emergent literacy among the children of Hispanic immigrants. *Arch Pediatr Adolesc Med*. 2000; 154(8):771-777.

5. Silverstein M, Iverson L, Lozano P. An English-language clinic-based literacy program is effective for a multilingual population. *Pediatrics*. 2002;109(5):E76-6.

6. Needlman R, Toker KH, Dreyer BP, Klass P, Mendelsohn AL. Effectiveness of a primary care intervention to support reading aloud: a multicenter evaluation. *Ambul Pediatr.* 2005;5(4):209–215.

7. Mendelsohn AL, Mogilner LN, Dreyer BP, et al. The impact of a clinic-based literacy intervention on language development in inner-city preschool children. *Pediatrics.* 2001;107(1):130–134.

8. High PC, LaGasse L, Becker S, Ahlgren I, Gardner A. Literacy promotion in primary care pediatrics: can we make a difference? *Pediatrics*. 2000;105(4 Pt 2):927-934.

9. Sharif I, Reiber S, Ozuah PO. Exposure to Reach Out and Read and vocabulary outcomes in inner-city preschool children. *J Natl Med Assoc*. 2002;94:171–177.

10. Diener ML, Hobson-Rohrer W, Byington, CL. Kindergarten readiness and performance of Latino children participating in Reach Out and Read. *J Community Med Health Edu*. 2012;2:133.

11. Council on Early Childhood; High, PC, Klass, P. Literacy promotion: an essential component of primary care pediatric practice. *Pediatrics*. Aug. 2014.;134(2):404-409.

12. Data Research Center for Child and Adolescent Health. 2011/12 National Survey of Children's Health. http://www.childhealthdata.org/browse/survey/results?q=2284&r=1&r2=51&g=470. Accessed November 28, 2016.

13. Children's Health Alliance of Wisconsin. Early literacy: Resources. http://www.chawisconsin.org/early-literacy.php?pg=38. Accessed November 28, 2016.

14. Dreyer BP, Mendelsohn AL, Tamis-LeMonda CS. Assessing the child's cognitive home environment through parental report: reliability and validity. *Early Dev Parent*. 1996;5:271- 287.

15. US Census Bureau. 2011-2015 American Community Survey 5-Year Estimates. Table S1501: Educational Attainment. 2015. https://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=ACS_14_5YR_S1501&prodType=table. Accessed Dec 15, 2016.

16. Child population by race and age group. KIDS COUNT Data Center. Annie E. Casey Foundation. http://datacenter.kidscount.org/data/tables/8446-child-population-by-race-and-age-group?loc=51&loct=2#detailed/2/51/false/869,36,868,867,133/68,69,67,12,70,66,71,13l/17077,17078. Updated August 2016. Accessed November 29, 2016.

17. US Census Bureau. 2011-2013 American Community Survey 3-year estimates. Table C16007: Age by Language Spoken at Home for the Population 5 Years and Over. 2013. http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=ACS_13_3YR_C16007&prodType=table. Accessed Dec 15, 2016.

Electronic Cigarette Exposure: Calls to Wisconsin Poison Control Centers, 2010–2015

Debora Weiss, DVM, MPH, MS; Carrie D. Tomasallo PhD, MPH; Jon G. Meiman, MD; Paul D. Creswell, PhD; Paul C. Melstrom, PhD; David D. Gummin, MD; Disa J. Patel, MPH; Nancy T. Michaud; Heather A. Sebero; Henry A. Anderson, MD

ABSTRACT

Background: E-cigarettes are battery-powered devices that deliver nicotine and flavorings by aerosol and have been marketed in the United States since 2007. Because e-cigarettes have increased in popularity, toxicity potential from device misuse and malfunction also has increased. National data indicate that during 2010–2014, exposure calls to US poison control centers increased only 0.3% for conventional cigarette exposures, whereas calls increased 41.7% for e-cigarette exposures.

Methods: We characterized cigarette and e-cigarette exposure calls to the Wisconsin Poison Center January 1, 2010 through October 10, 2015. We compared cigarette and e-cigarette exposure calls by exposure year, demographic characteristics, caller site, exposure site, exposure route, exposure reason, medical outcome, management site, and level of care at a health care facility.

Results: During January 2010 to October 2015, a total of 98 e-cigarette exposure calls were reported, and annual exposure calls increased approximately 17-fold, from 2 to 35. During the same period, 671 single-exposure cigarette calls with stable annual call volumes were reported. E-cigarette exposure calls were associated with children aged ≤5 years (57/98, 58.2%) and adults aged ≥20 years (30/98, 30.6%). Cigarette exposure calls predominated among children aged ≤5 years (643/671, 95.8%).

Conclusion: The frequency of e-cigarette exposure calls to the Wisconsin Poison Center has increased and is highest among children aged ≤5 years and adults. Strategies are warranted to prevent future poisonings from these devices, including nicotine warning labels and public advisories to keep e-cigarettes away from children.

• • •

Author Affiliations: Centers for Disease Control and Prevention (CDC), Center for Surveillance, Epidemiology, and Laboratory Services (CSELS), Office of Public Health Scientific Services, Atlanta GA (OPHSS); Epidemic Intelligence Service (Field) Officer, Madison, Wis (Weiss); Wisconsin Department of Health Services (DHS), Bureau of Environmental and Occupational Health, Madison, Wis (Anderson, Creswell, Michaud, Patel, Sebero, Tomasallo, Weiss); CDC, Field Services Branch, Madison, Wis (Meiman); University of Wisconsin School of Medicine and Public Health, Madison, Wis (Creswell, Michaud, Patel, Sebero); CDC, National Center of Chronic Disease Prevention and Health Promotion (NCCDPHP), Office on Smoking and Health (OSH), Epidemiology Branch (EB), Atlanta, GA (Melstrom); Wisconsin Poison Center, Children's Hospital of Wisconsin, Milwaukee, Wis (Gummin); Wisconsin DHS, Tobacco Prevention and Control Program, Madison, Wis (Michaud, Patel, Sebero).

Corresponding Author: Debora Weiss, 1 W Wilson St, Room 150, Madison, WI 53703; phone 608.266.6677; fax 608.267.4853; e-mail debora.weiss@wisconsin.gov.

INTRODUCTION

E-cigarettes are very popular and widely available members of a larger group of relatively new smoking devices called electronic nicotine delivery systems. In addition to e-cigarettes, these smoking devices include electronic hookahs, hookah pens, vapor pens (pen-like devices similar to e-cigarettes), and vaporizers, as well as electronic cigars and pipes.[1,2] E-cigarettes are metal or plastic tubes that contain a cartridge filled with an e-liquid (EL) solution that is aerosolized by a battery-powered heating element and simulated puffing.[3] ELs typically contain nicotine dissolved in propylene glycol, glycerine, or a mixture of the two,[4] and are available as an individual cartridge or as a refill solution for multiuse cartridges.[2] The aerosol generated from heating ELs can contain harmful substances (eg, diacetyl, formaldehyde, toxic metals, ultrafine particulate matter, and carcinogens).[5,6]

Findings from the 2014 National Youth Tobacco Survey indicated that e-cigarette use (ie, use ≥1/day during the past 30 days) among high school students had increased from 4.5% (approximately 660,000 students) during 2013 to 13.4% (2 million students). Among middle school students e-cigarette use more than tripled, from 1.1% during 2013 to 3.9% during 2014, an increase from approximately 120,000 students to 450,000 students.[7] A consumer-based survey reported a 4-fold increase in the proportion of adults who had tried e-cigarettes between 2009 and 2010.[8] In 2014, the National Health Interview Survey from the National Center for Health Statistics reported that 12.6% of adults had tried e-cigarettes. Furthermore, among cigarette smokers who had tried to quit smoking during the previous year, approximately 50% had tried e-cigarettes and 20.3% were current e-cigarette users.[9]

A particular area of public health concern is how increased availability of e-cigarettes might affect children. These prod-

ucts can be appealing to children because ELs often contain candy-like flavors.[10] Accidental ingestion of nicotine-containing products can cause nicotine poisoning,[8,11] which can result in nausea, vomiting, agitation, confusion, diaphoresis, cardiac arrhythmias, coma, and death.[11] Among children, nicotine toxicity can occur with ingestion of 10–30 mg of nicotine, corresponding to 1 whole conventional cigarette or as little as 1 mL of 36 mg/mL nicotine-containing EL.[8] In January 2016, the Child Nicotine Poisoning Prevention Act was signed into law. This law mandates childproofing of EL containers that contain nicotine.[12] In the absence of this law, childproofing EL products had been voluntary. Product labeling is not covered by this law, and studies have reported that labels are often an inaccurate reflection of EL contents.[13,14]

National studies of poison center data have reported an increasing trend in calls to poison control centers related to e-cigarettes, with a disproportionate percentage of exposures occurring among young children.[8,15] Calls to the poison centers regarding exposures in children are often placed when any exposure or possible exposure to e-cigarettes or cigarettes has occurred, whereas calls to poison centers about adult exposures are placed mainly because of symptoms of poisoning. We examined frequency of calls to the Wisconsin Poison Center during 2010–2015 for e-cigarette exposures and characterize exposures and associated adverse health effects, compared with calls for conventional cigarette exposures.

Figure 1. Number of Calls to the Wisconsin Poison Center for E-cigarette and Cigarette Exposures by Year, January 2010–October 2015

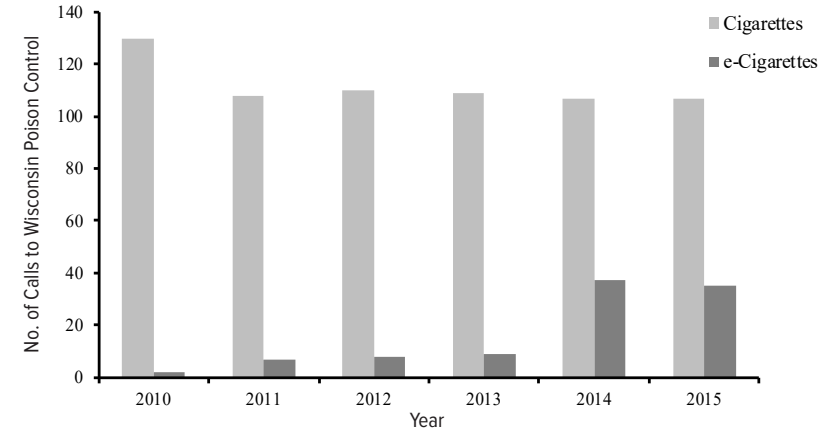
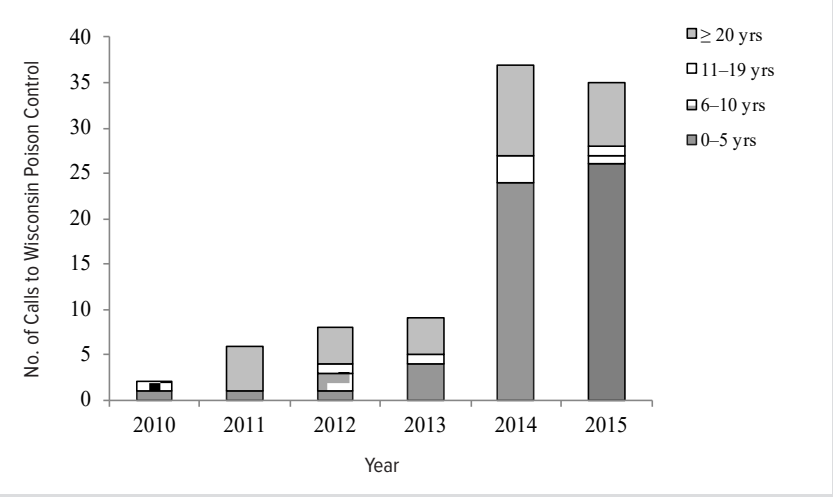


Figure 2. Annual E-cigarette Exposure Calls to the Wisconsin Poison Center by Age Category of the Exposed Person, January 2010–October 2015

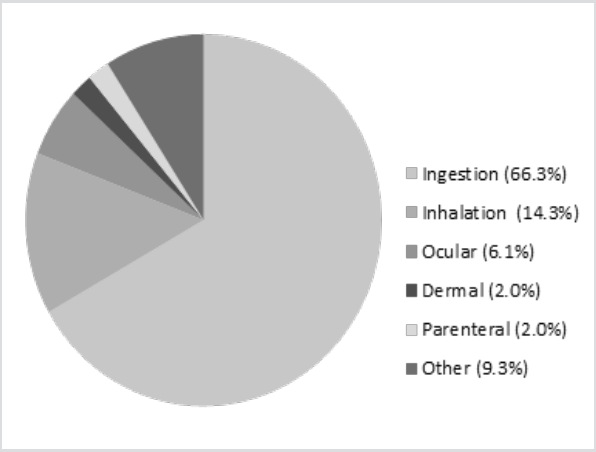


METHODS

We carried out a retrospective review of suspected cigarette and e-cigarette poisonings reported to the Wisconsin Poison Center, a designated regional poison control center located at the Children's Hospital of Wisconsin (Milwaukee, Wisconsin) during January 1, 2010 to October 10, 2015. The Wisconsin Poison Center is staffed 24 hours per day with personnel specifically trained to provide advice regarding suspected poisonings. Personnel perform standardized interviews, electronically record pertinent case information, and upload summary information into the National Poison Data System. The latter served as the primary data source for this study. This data were supplemented with information abstracted from case narratives for all e-cigarette poisoning calls to provide additional details.

An e-cigarette exposure call was defined as a call to the Wisconsin Poison Center for a possible exposure to an e-cigarette, e-cigarette cartridge, or EL. A cigarette exposure call was defined as a call for a possible exposure to tobacco cigarettes or butts. An exposure was defined as any actual or suspected contact with any substance regardless of toxicity or clinical manifestation. Only calls initially classified as exposures by poison center personnel were included in the analysis. Cases initially thought to be exposures were included even if confirmed as nonexposures later (n=4). Calls regarding multiple exposures (eg, cigarettes and ethanol) were excluded from the study,

Figure 3. E-cigarette Exposures by Route (N=98)



because they were limited (n=7), and our focus was exclusively e-cigarette poisonings.

Cigarette and e-cigarette exposure groups were compared by year of exposure, demographic characteristics, caller site, exposure site, exposure route, exposure reason, medical outcome, management site, and level of care at a health care facility. These categories (Table 1) follow the National Poison Data System coding scheme developed by the American Association of Poison Control Centers.[16]

RESULTS

The Wisconsin Poison Center received 98 e-cigarette and 671 cigarette exposure calls January 1, 2010 through October 10, 2015. Annual number of calls for e-cigarette exposures increased from 2 during 2010 to 35 during 2015 (as of October), a >17-fold increase (Figure 1). When reviewing e-cigarette and conventional cigarette exposures combined, e-cigarette exposures accounted for 1.5% of calls during 2010, compared with 25.7% of calls during 2014, also an approximately 17-fold increase. The annual number of calls for cigarette exposures remained stable during this period (Figures 1, 2).

As displayed in Figure 2, e-cigarette exposures occurred primarily among individuals ≤5 and ≥20 years of age. The proportion of e-cigarette exposures among children ≤5 years of age, compared with other age groups, increased during the study period (Figure 2). During the same timeframe, cigarette exposures occurred primarily among children ≤5 years of age. E-cigarette exposures occurred mostly among males, while conventional cigarette exposures were distributed approximately evenly between males and females. Similar trends by sex were observed among children ≤5 years of age, for both e-cigarette and cigarette exposure. Most e-cigarette and cigarette exposures occurred at the patient's home, therefore it is not surprising that most exposure calls for both study groups originated from the exposed person's residence. Predominant exposure routes for e-cigarettes were ingestion, followed by inhalation, ocular, and dermal, as well as parenteral exposures (Figure 3). Combined exposures (eg, ingestion and dermal) were few and categorized as "Other." For conventional cigarettes, ingestion and inhalation were the only exposure routes.

In our analysis, the majority of exposures among patients ≤5 years of age were from the ingestion of EL during an unsupervised period. Exposures among patients ≥20 years of age were mainly unintentional because of malfunction of the e-cigarette resulting in ingestion of EL while attempting to smoke. Ocular exposures also occurred in this age category, because of some patients mistakenly using the EL container as eye drops or accidentally spraying EL in the eye while attempting to refill an e-cigarette. Intentional misuse such as deliberate ingestion or intravenous injection of EL also happened in a small number of e-cigarette exposures (Table).

Case report reviews revealed that for a number of e-cigarette exposure calls, the Wisconsin Poison Center personnel were uncertain of the level of exposure and had to look to external sources (eg, the websites of EL manufacturers) to get information about what chemicals and dose to which persons might have been exposed.

With regard to medical outcome, a majority of individuals with exposures to e-cigarettes and cigarettes were asymptomatic or had symptoms of limited severity. Minor, rapidly resolving symptoms frequently involving mucous membranes were observed in approximately one-third of e-cigarette and cigarette exposures. Moderate effects, defined as patients having more prolonged or systemic symptoms that required treatment, occurred among 4.1% e-cigarette and <1.0% cigarette exposures. For approximately one-fourth of e-cigarette and cigarette exposures, the medical outcomes were not known or were determined to be unrelated to the exposure.

Among e-cigarette and cigarette exposures that resulted in either minor or moderate effects, emesis was the predominant adverse effect, mainly because of ingestion of EL or cigarettes or cigarette butts. Coughing and choking was also a notable adverse effect of cigarette exposures, but this was not an observed consequence of e-cigarette exposures. One patient in our study had an acute allergic reaction after using a cinnamon flavored e-cigarette. The manufacturer eventually stopped production of this EL because of potential adverse health effects from the cinnamon flavoring.[17]

Moderate effects resulting from e-cigarette exposures occurred among 3 adults and 1 child. One patient fell asleep and EL containing 100 mg of nicotine spilled on his abdomen and arm. This patient experienced nausea, vomiting, headache, and abdominal pain and was treated at an emergency department and released after symptoms ceased. Another exposure resulting in a moderate effect occurred when a person possibly injected EL intravenously with a 100 mL syringe. The emergency department provided supportive care for diaphoresis and pallor. He was later admitted to the psychology department. A moderate effect also occurred in an

asthmatic child age 6 years who took a puff from an e-cigarette resulting in bronchospasm and coughing. The child's symptoms were managed at home with a nebulizer. Finally, an adult experienced chest pain after inhaling EL when his e-cigarette malfunctioned. The patient was evaluated at an emergency department, released, and lost to follow-up.

Most patients were safely managed at home after exposures to either e-cigarettes or cigarettes. At the time of call to the Wisconsin Poison Center, some patients were already en route to a health care facility. Poison center personnel referred a small number of patients to a health care center. Most patients who were referred to, or were already en route to a health care facility at the time of call were exposed to e-cigarettes (Table).

DISCUSSION

E-cigarettes have been marketed in the United States since 2007. Between 2010 and October 2015, there was an approximate 17-fold increase in annual e-cigarette exposure calls to the Wisconsin Poison Center. The trend is similar to that seen in recent national data. The increase in annual e-cigarette exposure calls coincides with an increase of e-cigarette use, especially between 2013 and 2014.[7]

Our study reported that the highest percentage of calls for e-cigarette exposures were for children ≤5 years of age, followed by adults ≥20 years of age. This trend is similar to national studies, which reported e-cigarette exposures were more frequent among children ≤5 years of age,[8,18-20] followed by adults between age 20–39 years.[8] The majority of exposures among these age groups resulted in none or minor effects. This finding is supported by a study concerning e-cigarette exposure calls to Texas poison centers, which also reported that the majority of exposures resulted in minor effects.[19] Interestingly, exposures to e-cigarettes occurred predominantly among males in this analysis, a finding that was not observed in similar studies.[18-19] Most exposures among children ≤5 years of age occurred at and were well managed at home. Our results are consistent with a study in which approximately 80% of e-cigarette exposures occurred at the residence of the exposed person.[8] This result is expected, because 1 study reported that most daily e-cigarette users smoke at home and refill their e-cigarette ≥5 times per day.[21]

The site of exposure management varied between the 2 study groups. Compared with cigarette exposure calls, a larger proportion of calls regarding e-cigarette exposures were placed while en route to a health care facility. We hypothesize that because of ambiguous labeling and novelty of e-cigarettes and ELs, the exposure was perceived as a substantial threat to the exposed individual's health that warranted visiting a health care facility versus calling the poison center.

Our study reported that toxicity assessment and responses by Wisconsin Poison Center personnel were complicated by incon-

Table. Wisconsin Poison Center (WPC) Calls by Caller Site, Exposure Site, Exposure Route, Reason for Exposure, Medical Outcome, Management Site, and Level of Care at a Health Care Facility, January 2010–October 2015

	E-cigarette Total N=98	%	Cigarette Total N=671	%
Caller Site				
Own residence	70	71.4	550	82.0
Health care facility (HCF)	18	18.4	45	6.7
Other	7	7.1	50	7.5
Workplace	3	3.1	6	0.9
Other residence	—	—	18	2.7
School	—	—	1	0.1
Public area	—	—	1	0.1
Exposure Site				
Own residence	89	90.8	612	91.2
Other residence	4	4.1	39	5.8
Workplace	2	2	—	—
Health care facility (HCF)	1	1	—	—
School	1	1	1	0.1
Public area	1	1	9	1.3
Other	—	—	7	1
Unknown	—	—	3	0.7
Exposure Route				
Ingestion	65	66.3	667	99.4
Inhalation and nasal	14	14.3	4	0.6
Ocular	6	6.1	—	—
Ingestion and dermal	5	5.1	—	—
Dermal	2	2	—	—
Ingestion, inhalation and nasal	2	2	—	—
Parenteral	2	2	—	—
Ingestion and ocular	1	1	—	—
Inhalation, nasal and dermal	1	1	—	—
Exposure Reason				
Unintentional — general	71	72.4	658	98.1
Unintentional — misuse	11	11.2	3	0.4
Unintentional — therapeutic error	3	3.1	—	—
Intentional — misuse	5	5.1	2	
Intentional — abuse	2	2	1	0.1
Intentional — suspected suicide	1	1	—	—
Intentional — unknown	—	—	3	0.4
Adverse reaction — other	4	4.1	1	0.1
Other — contamination or tampering	1	1	3	0.4
Medical Outcome				
No effect	37	37.8	312	46.5
Minor effect	37	37.8	178	26.5
Moderate effect	4	4.1	5	0.7
Not followed, minimal clinical effects possible	13	13.3	126	18.8
Not followed, judged as nontoxic exposure	2	2.0	21	3.1
Unable to follow, judged as a potentially toxic exposure	3	3.1	11	1.6
Unrelated effect, exposure was probably not responsible for effect	2	2.0	14	2.1
Confirmed nonexposure	—	—	4	0.6
Management Site				
Patient was managed on site (non-HCF)	62	63.3	603	89.9
Patient en route to/in HCF when WPC called	21	21.4	43	6.4
Patient was referred by WPC to a HCF	15	15.3	22	3.3
Other	—	—	1	0.1
Unknown	—	—	2	0.3
Level of Health Care Facility Care				
Evaluated, treated and released	20	20.4	55	8.2
Patient lost to follow-up or left against medical advice	7	7.1	9	1.3
Patient refused referral or did not arrive at HCF	5	5.1	—	—
Admitted to non-critical care unit	1	1.0	1	0.1
Unknown	65	66.3	606	90.3

sistent and misleading labeling of EL containers. In multiple e-cigarette cases, personnel had difficulty identifying the actual nicotine dose ingested to determine whether it might have been toxic to the person. Labels on numerous EL containers do not state concentration, nor specify whether the amount of nicotine listed on the label refers to the concentration or total amount of nicotine in the EL container. In certain cases, poison center personnel had to refer to the EL manufacturer's website to determine nicotine concentration. This was complicated by the fact that the concentration of nicotine listed on the labels of EL containers can be markedly different from measured values.[5]

This study has certain limitations. The Wisconsin Poison Center is dependent on self-reported exposures. Potential for case ascertainment bias exists, because exposures among children generally are more likely to be reported than those among adults. This is because, essentially, concerns about potential poisonings in children are more worrisome than concerns about potential poisonings in adults. As mentioned in a previous study,[8] variations among poison center personnel in categorizing cases has been noted, leading to miscoding of exposure characteristics. Furthermore, not all exposures to e-cigarette and cigarettes may have been reported to the Wisconsin Poison Center. Lastly, a small number of calls regarding an exposure to e-cigarettes or cigarettes paired with another type of exposure were excluded from this analysis. Because of these factors, the e-cigarette exposures reported here are likely an underestimate of all exposures among the general population.[8]

CONCLUSIONS

The increase in unintended child exposures to e-cigarettes warrants robust public health surveillance of e-cigarette use and adverse events. Future studies will determine if child proofing substantially reduces the number of child poisoning incidents. Incomplete or inaccurate labeling delays emergency department or poison control personnel from implementing correct and potentially lifesaving treatments.

Reminding the public to keep ELs and e-cigarettes away from children is critical. Furthermore, implementation of national strategies to prevent future exposures, such as consistent product content labeling, is urgently needed.

Acknowledgements: The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention. The authors extend appreciation to Christy Vogt, MPH, and Megan Christenson, MS, MPH, for earlier revisions of this manuscript.

Funding/Support: None declared.

Financial Disclosures: None declared.

REFERENCES

1. Brandon TH, Goniewicz ML, Hanna NH, et al. Electronic nicotine delivery systems: a policy statement from the American Association for Cancer Research and the American Society of Clinical Oncology. *J Clin Oncol*. 2015;33(8):952-963.

2. King BA, Patel R, Nguyen KH, Dube SR. Trends in Awareness and Use of Electronic Cigarettes among U.S. Adults, 2010-2013. *Nicotine Tob Res.* 2015;17(2):219-227.

3. Brown CJ, Cheng JM. Electronic cigarettes: product characterisation and design considerations. Tob Control. 2014;23:ii4-ii10.

4. Han S, Chen H, Zhang X, Liu T, Fu Y. Levels of selected groups of compounds in refill solutions for electronic cigarettes. *Nicotine Tob Res*. 2016; 18(5): 708-714.

5. Westenberger BJ. Evaluation of e-cigarettes [memo]. St Louis, MO: Department of Health and Human Services, Food and Drug Administration CfDEaR, Division of Pharmaceutical Analysis; May 4, 2009. http://www.fda.gov/downloads/drugs/Scienceresearch/UCM173250.pdf. Accessed December 16, 2016.

6. Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. PLOS One. 2013;8(3):e57987.

7. E-cigarette use triples among middle and high school students in just one year [news release]. Atlanta, GA; Centers of Disease Control and Prevention; April 16, 2015. https://www.cdc.gov/media/releases/2015/p0416-e-cigarette-use.html. Accessed December 2, 2016.

8. Vakkalanka JP, Hardison LS Jr, Holstege CP. Epidemiological trends in electronic cigarette exposures reported to U.S. Poison Centers. *Clin Toxicol* (Phila). 2014;52(5):542-548.

9. Schoenborn CA, Gindi RM. Electronic Cigarette Use Among Adults: United States, 2014. Atlanta, GA: U.S. Centers for Disease Control and Prevention; NCHS Data Brief No. 217; October 2015. http://www.cdc.gov/nchs/products/databriefs/db217.htm. Assessed Dec 9, 2016.

10. Choi K, Fabian L, Mottey N, Corbett A, Forster J. Young adults' favorable perceptions of snus, dissolvable tobacco products, and electronic cigarettes: Findings from a focus group study. *Am J Public Health*. 2012;102(11):2088-2093.

11. McGee D, Brabson T, McCarthy J, Picciotti M. Four-year review of cigarette ingestions in children. *Pediatr Emerg Care*. 1995;11(1):13-16.

12. Child Nicotine Poisoning Prevention Act of 2015, S. 142, 114th Cong. (2016). https://www.congress.gov/bill/114th-congress/senate-bill/142. Accessed Dec 2, 2016.

13. Rutledge R. Gasping for action | A watchdog report: Lab tests reveal popular e-cigarette liquids contain harmful chemicals. *Milwaukee Journal Sentinal*. October 20, 2015.

14. Trtchounian A, Talbot P. Electronic nicotine delivery systems: Is there a need for regulation? *Tob Control*. 2011;20(1):47-52.

15. Cobb NK, Byron MJ, Abrams DB, Shields PG. Novel nicotine delivery systems and public health: the rise of the "e-cigarette." *Am J Public Healt*h. 2010;100(12):2340-2342.

16. American Association of Poison Control Centers (AAPCC). National Poison Data System (NPDS) Coding Users' Manual. Ver 3.1. Alexandria, VA: AAPCC; 2014.

17. Tasty Vapor Mix Team. Time to say farewell to a tasty classic. Tasty Vapor. http://www.tastyvapor.us/blog/atomic-cinnacide-retirement/#. Posted June 11, 2015. Accessed December 6, 2016.

18. Chatham-Stephens K, Law R, Taylor E, et al; Centers for Disease Control and Prevention. Notes from the field: calls to poison centers for exposures to electronic cigarettes — United States, September 2010–February 2014. *MMWR Morb Mortal Wkly Rep*. 2014;63(13):292-293.

19. Ordonez JE, Kleinschmidt KC, Forrester MB. Electronic cigarette exposures reported to Texas poison centers. *Nicotine Tob Res*. 2015;17(2):209-211.

20. Dotinga R. E-Cigarette Poisonings Skyrocket Among Young Kids: Study. *Health Day*. May 9, 2016. https://consumer.healthday.com/cancer-information-5/tobacco-and-kids-health-news-662/e-cigarette-poisonings-among-kids-skyrocket-study-710673.html. Accessed Dec 10, 2016.

21. Etter JF, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction*. 2011;106(11):2017-2028.

Hemodynamics During Dialysis and Changes in Cognitive Performance

Dawn Wolfgram, MD; Elisabeth Vogt, MS; Allison L. Jahn, PhD; Heather M. Smith, PhD, ABPP; Joleen Sussman, PhD; Alexis Visotcky, MS; Purushottam Laud, PhD; Jeff Whittle, MD, MPH

ABSTRACT

Introduction: Hemodialysis (HD) patients are at increased risk for cognitive impairment. Blood pressure (BP) fluctuations during HD may affect cerebral perfusion and subsequently cognitive function.

Objective: Examine and provide information on the relationship between intradialytic hemodynamics and cognitive outcomes over a 1-year period.

Methods: HD patients without diagnosed dementia who were 50 years old or older were given a neurocognitive battery at baseline and at 1-year follow-up. Over the 1-year period, we collected demographic and laboratory data, as well as dialytic BP and ultrafiltration rate (UFR) measurements and tested the association between changes in cognitive test scores and intradialytic hemodynamics, adjusting for demographic and clinical variables.

Results: Thirty-nine participants enrolled in the study and 32 remained at 1-year follow-up. The mean (SD) age was 66.8 (10.0) years. Hypertension was present in 100% and diabetes mellitus in 47% of the cohort. The average change in systolic BP from predialysis to postdialysis was -9.9 (16.3) mmHg, and average maximum drop in systolic BP during dialysis was 27.9 (10.2) mmHg. Overall, the cognitive test scores did not have significant changes from baseline to 1 year. In our linear regression analysis there was no association between the BP measures and cognitive changes, although UFR was associated with change in performance on a test of executive functioning.

Conclusions: In prevalent HD patients, cognitive function was generally stable over a 1-year period, and there was no association with intradialytic hemodynamic variables.

• • •

Author Affiliations: Medicine Division, Section of Nephrology, Clement J. Zablocki VA Medical Center, Milwaukee, Wis (Wolfgram); Department of Medicine, Division of Nephrology, Medical College of Wisconsin (MCW), Milwaukee, Wis (Wolfgram); Department of Clinical Psychology, Marquette University, Milwaukee, Wis (Vogt); Mental Health Division, Clement J. Zablocki VA Medical Center and Department of Psychiatry and Behavioral Medicine, MCW (Jahn, Smith); VA Eastern Colorado Health Care System (Sussman); Institute for Health and Society, Division of Biostatistics, MCW (Visotcky, Laud); Primary Care Division, Clement J. Zablocki VA Medical Center (Whittle); Department of Medicine, Division of General Internal Medicine, MCW (Whittle).

Corresponding Author: Dawn Wolfgram, MD, Department of Medicine, Medical College of Wisconsin, 9200 W Wisconsin Ave, Clinical Cancer Center, Milwaukee, WI 53226; phone 414.384.2000 ext 4-2825; fax 414.383.9333; e-mail dwolfgram@mcw.edu.

INTRODUCTION

Cognitive impairment is common in patients receiving hemodialysis (HD) for end-stage renal disease (ESRD).[1] Among individuals with ESRD, cognitive impairment is associated with increased mortality and health care costs, and decreased quality of life.[2-4] Unfortunately, cognitive impairment appears to worsen in patients receiving HD. Furthermore, with our aging dialysis population, cognitive impairment may become more prevalent as age is a risk factor for cognitive decline. An analysis of United States Renal Data System data reveals a significant increase in incident dementia following initiation of HD, specifically when compared to patients with ESRD on peritoneal dialysis.[5] A small longitudinal study demonstrated that HD patients had greater decline in Mini-Mental Status Exam than age-matched controls.[6]

Beyond traditional risk factors, it is not clear why the HD population disproportionately experiences cognitive impairment. Although chronic kidney disease is associated with cognitive impairment,[7] aspects of the HD process may additionally contribute directly to cognitive decline.[1,8] Since HD is often characterized by large swings in blood pressure (BP),[9] it has been hypothesized that drops in BP may lead to periods of decreased cerebral perfusion, which cumulatively lead to ischemic injury, atrophy, and subsequent cognitive decline.[8,10] Previous studies using transcranial doppler monitoring have shown that cerebral blood flow decreases during HD.[11] Moreover, brain imaging of persons on HD reveals more atrophy, silent infarcts, and white matter disease than that of age-matched control subjects not on dialysis.[12,13]

We previously reported that there was no association between cognitive performance and intradialytic BP variability in a cross-sectional study.[14] However, given limitations of cross-sectional data, we conducted a 1-year prospective study to better character-

Table 1. Baseline Demographics and Characteristics of the Cohort

Variable	Mean (SD) or N (%)
Age (years)	66.8 (10.0)
Race	
White	8 (25.0)
African American	21(65.6)
Native American	2 (6.3)
Other	1 (3.1)
Sex	
Male	27 (84.4)
Duration of Dialysis (years)	
4.47 (4.3)	
Education Level	
1-12 years	16 (50.0)
Vocational/trade/some college	9 (28.1)
College or more	7 (21.9)
Employment Status	
Unemployed	3 (9.4)
Employed	7 (21.9)
Retired	22 (68.8)
Comorbidities	
Diabetes Mellius	15 (46.9)
Hypertension	32 (100)
Congestive heart failure	10 (31.3)
Coronary artery disease	8 (25.0)
Peripheral vascular disease	3 (9.4)
Stroke	4 (12.5)
Primary Cause of End-Stage Renal Disease	
Diabetes Mellitus	12 (37.5)
Hypertension	11 (34.4)
Glomerulonephritis	3 (9.4)
Other	6 (18.8)
Duration of Hemodialysis Session (hours)	3.8 (0.5)
Laboratory Values (average of baseline and 12 months)	
Hemoglobin (mg/dl)	10.8 (1.4)
Albumin (g/dl)	3.9 (0.4)
Kt/V	1.5 (0.2)
Dialytic Hemodynamics Over the 1-Year Period	
Change in pre- to postsystolic blood pressure (mmHg)	-9.9 (16.3)
Change in pre- to postdiastolic blood pressure (mmHg)	-3.3 (5.9)
Maximum decrease in systolic blood pressure (mmHg)	27.9 (10.2)
Maximum decrease in diastolic blood pressure (mmHg)	16.9 (5.4)
Average minimum systolic blood pressure (mmHg)	112.3 (13.3)
Average minimum diastolic blood pressure (mmHg)	60.6 (13.9)
Ultrafiltration rate (ml/kg/hour)	9.6 (2.8)

Laboratory values and dialytic hemodynamics are averaged over the 1-year period; the remaining characteristics are from baseline.

ize and provide further information on the relationship between intradialytic hemodynamics and changes in cognitive performance over time.

METHODS

Study Population

After approval from the Milwaukee VA Medical Center and Medical College of Wisconsin Institutional Review Board, we recruited patients >50 years of age who were receiving thrice weekly chronic HD at one of 3 Milwaukee area dialysis centers. We excluded patients with diagnosed dementia, Parkinson's disease, intracranial tumor or bleed within the previous 12 months, or traumatic brain injury. Additionally, we excluded patients who lacked stamina to undergo a 1-hour neuropsychological test battery. All participants provided written informed consent before beginning study procedures, and research was carried out according to the principles of the Declaration of Helsinki.

Data Collection Procedure

Participants completed a written survey regarding sociodemographics (eg, age, race, education, and employment status), duration of hemodialysis, and their personal history of hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, peripheral vascular disease, cirrhosis, and stroke. The presence or absence of comorbid conditions was confirmed using the medical record, and the primary cause of renal disease was obtained from the ESRD Registration Report. We collected hemoglobin and albumin values and a marker of dialysis adequacy (Kt/V) during the month of baseline and 12-month cognitive testing from the dialysis center medical records.

Two nephrologists obtained the ultrafiltration rate (UFR) and all sitting BP measurements (predialysis BP, dialytic BPs, and postdialysis BP) for 3 consecutive dialysis sessions at baseline and 3, 6, 9, and 12 months follow-up for a total of 15 sessions. These measurements are routinely collected every 15 to 20 minutes at our dialysis facilities. For each dialysis session, we calculated the minimum BP (lowest BP from any BP readings during dialysis, including pre- and postmeasurements), the maximum decrease in BP (predialysis BP minus the lowest BP for each dialysis session), and the change in BP from predialysis to postdialysis (predialysis BP minus the postdialysis BP) for both systolic (SBP) and diastolic BP (DBP), as well as the UFR (net amount of fluid [ml] removed divided by weight [kg] divided by the duration of dialysis [hours]). We then averaged each of these measures of intradialytic hemodynamics across all sessions for each patient.

Neurocognitive Testing

Trained study team members administered a battery of neurocognitive tests to each participant using standardized procedures. The battery assessed the following domains: executive functioning, memory, learning, language, and attention. The Montreal Cognitive Assessment (MoCA) was used to assess global cognitive functioning. The remainder of the neurocognitive battery included the Hopkin's Verbal Learning Test-Revised (HVLT-R), Trail Making Test A and B, Controlled Oral Word Association Test (COWAT), Animal Naming, and the Wechsler Adult Intelligence Scale-Fourth Edition Digit Span subtest. Cognitive domains assessed by each test are noted in the Results section. The Advanced Clinical Solutions Test of Premorbid Functioning also was included to estimate premor-

bid intelligence.[15] The Test of Premorbid Functioning accounts for age, gender, education level, self and parental occupation, religion, geographic area, and community environment both currently and during childhood. Cognitive testing was done after dialysis in 30 participants and prior to dialysis in 2 participants at baseline. Follow-up testing was completed on the same time schedule (postdialysis or predialysis) as the first testing session, except for 2 participants who changed from postdialysis to an off day for their convenience. On average, the neurocognitive battery took 40 minutes to complete. Published age, gender, education, and ethnicity corrected norms were used to score the neuropsychological tests.[16-19]

Table 2. Changes in Cognitive Test Scores From Baseline to 12 Months

Test (N)	Domain	Baseline	12 month	Change in Score	*P*-value[a]
MoCA Score (32)	Cognitive screen	21.8 (3.8)	21.7 (3.9)	-0.2(2.8)	0.84
Hopkin Verbal Learning					
Immediate (31)	Immediate memory	32.1 (9.8)	29.6 (8.2)	-2.5 (7.2)	0.27
Delayed (31)	Delayed memory	29.6 (10.9)	29.1 (9.7)	-0.5 (6.8)	0.86
Recognition (31)	Recognition memory	39.1 (14.1)	43.4 (12.2)	4.3 (13.4)	0.21
Trails A (30)	Simple attention, processing speed	40.6 (10.9)	43.9 (11.8)	3.3 (6.8)	0.27
Trails B (29)	Executive function, processing speed	39.5 (11.4)	42.9 (10.7)	3.4 (8.7)	0.26
COWAT (30)	Executive function, verbal fluency (phonemic), memory	43.1 (10.1)	41.1 (10.4)	-2.0 (7.0)	0.45
Animal Naming (30)	Executive function, verbal fluency (semantic), memory	46.4 (9.7)	46.7 (13.2)	0.3 (10.6)	0.93
Digit Span Total (31)	Working memory, attention	8.1 (2.7)	8.1 (2.5)	0.0(1.8)	1.00

[a]*P*-value comparing baseline to 12-month scores based on *t*-test.
Abbreviations: MoCA, Montreal Cognitive Assessment; COWAT, Controlled Oral Word Association Test.

Statistical Analysis

We calculated characteristics of the participants as means (SD) for continuous measures and frequencies for categorical data. Cognitive test scores at baseline and at 12-month follow-up were calculated with standard methods, then subtracted to yield the outcome variables – change in cognitive function. We compared the scores of the cohort at baseline and 12 months using *t*-tests. Based on our initial finding of little change in cognitive test scores over 1 year for the full cohort, we also evaluated participants with less than 1 year of dialysis separately. We tested the association between BP fluctuation and change in cognitive test scores by linear regression. Our analysis centered on SBP as it has shown to be a predictor of clinical outcomes in people over 50 years.[20]

Due to the exploratory nature of the study, we did evaluate the association of each hemodynamic variable with the change in each cognitive test score in parallel analyses. A Benjamini-Hochberg false discovery rate adjustment was used to account for significance testing of 36 associations. If the association between a measure of BP fluctuation and a measure of change in cognition was significant (adjusted *P*-value <0.05) in a simple linear regression analysis, the association was then tested in a multivariable regression model that adjusted for age, race (ie, white or not), presence of diabetes, and hemoglobin level (average of baseline and 12 months). We chose covariates based on prior work demonstrating an association with cognitive function in the dialysis population.[3,14] SAS V 9.2 (SAS Institute Inc, Cary, North Carolina) was used for the statistical analysis.

RESULTS

Demographic and Clinical Characteristics

Thirty-nine participants completed the baseline testing and 32 completed the 1-year follow-up testing. Of the 7 participants who did not complete follow-up testing, one relocated, three died, one transferred to peritoneal dialysis, one underwent treatment for lymphoma complicated by infection and delirium (an exclusion criteria), and one declined follow-up testing due to inconvenience. The mean (SD) age of the 32 participants who completed the follow-up testing was 66.8 (10.0) years, and diabetes mellitus and hypertension were present in 47% and 100% of participants, respectively (Table 1).

Intradialytic Hemodynamics

The mean intradialytic SBP ranged from 94 mmHg to 165 mmHg (mean [SD] 133.3 [16.5]). The mean maximum intradialytic SBP ranged from 127mmHg to 198 mmHg (mean [SD] 167.6 [18.8]). See Table 1 for the mean and SD of each measure of BP fluctuation and the UFR for our cohort. BP fluctuation among participants who dropped out was not statistically different from fluctuation among those who completed the study (data not shown).

Cognitive Outcomes for Full Cohort

Overall, a high degree of cognitive impairment was observed at baseline, with almost 60% of the cohort scoring 2 SDs below the population mean on the screening measure of global cognitive function (MoCA).[14] The Test of Premorbid Functioning score (mean [SD]) was not statistically different from the predicted score (87.3 [10.6] vs 91.7[8.9], *P*=0.08), indicating that our cohort's observed impairment reflected a decline from premorbid functioning. Mean test scores for our cohort did not change significantly from baseline to follow-up (Table 2). There was no significant decline in any of the cognitive scores from baseline to follow-up. Indeed, in some cases, there was nonsignificant improvement. To further explore our data, we then examined the

Table 3. Comparison of the Change in Cognitive Test Scores for Participants With <1 Year of Dialysis at the Start of the Study to Participants With ≥1 Year of Dialysis

	Change in Score (SD) for Participants With <1 Year of Dialysis (N=9)	Change in Score (SD) for Participants With ≥1 Year of Dialysis (N=23)
MoCA score	-0.6 (2.9)	0.0 (2.8)
Immediate norm	-5.2 (8.4)	-1.5 (6.5)
Delayed norm	-0.8 (7.8)	-0.3 (6.6)
Recognition norm	4.8 (11.7)	4.0 (14.3)
Trails A norm	1.1 (4.6)	4.2 (7.5)
Trails B norm	1.3 (7.5)	4.4 (9.3)
COWAT norm	-2.3 (8.1)	-1.9 (6.8)
Animal Naming *t*-score	3.2 (11.5)	-1.1 (10.1)
Digit Span Total norm	0.1 (1.9)	0.0 (1.8)

Abbreviaions: MoCA, Montreal Cognitive Assessment; COWAT, Controlled Oral Word Association Test.
Laboratory values and dialytic hemodynamics are averaged over the 1-year period; the remaining characteristics are from baseline.

9 participants who we enrolled within 1 year of starting HD. In those patients there was a more uniform tendency of cognitive scores decrease. Specifically, for the cognitive tests that did have a decrease in score from baseline, the mean change (SD) in MoCA was -0.6 (2.9) vs 0.0 (2.8), in Hopkins Immediate memory was -5.2 (8.4) vs -1.5 (6.5), in Hopkins Delayed memory was -0.8 (7.8) vs -0.3 (6.6), and in COWAT -2.3 (8.1) vs -1.9 (6.8) for the 9 participants vs the remaining 23 participants, respectively (Table 3). None of these comparisons were significant.

Relationship Between Intradialytic Hemodynamics and Cognitive Outcomes

There was no significant association between intradialytic BP variables and changes in cognitive test scores in univariable analysis. However, a higher UFR was associated with improvement in performance on Trails B (a test of executive functioning) in both bivariate (Table 4) and multivariable analysis. In the multivariable analysis every 1 ml/kg/hr increase in UFR was associated with 2.4-point positive change in Trails B score over the study year ($P<0.01$). This association persisted after we adjusted for Kt/V in our model.

DISCUSSION

Contrary to our hypothesis that cognitive decline in the dialysis population is mediated by intradialytic hemodynamic fluctuation, we found no association between intradialytic BP variability and changes in cognitive performance. Moreover, we found that higher average UFR, a surrogate for rapid fluid removal, was associated with improvement rather than deterioration in performance on Trails B, a test of executive functioning. Finally, we did not see the expected drop in cognitive status over the study period.

Although it has been postulated that hemodynamic fluctuations during dialysis may contribute to cognitive dysfunction,[1,8,10,21] ours is the first longitudinal analysis to directly address the relationship between hemodynamics during dialysis and long-term changes in cognitive status. Previous evaluations of the impact of intradialytic hemodynamics on cognitive performance are limited to cross-sectional analyses, which cannot account for the impact of prior hemodynamic fluctuations on cognitive impairment.[14,22,23] In a cross sectional analysis of the Frequent Hemodialysis Network Trial (FHNT) that evaluated correlates of cognitive impairment, investigators did not find that hemodynamic variables of predialysis BP or need for intravenous saline for hypotension during dialysis were associated with cognitive impairment.[23] Additionally, in the FHNT, the ultrafiltration volume (in ml/kg) was not associated with a Trails B score; however, this study used a cutoff score to designate impairment in Trails B and did not adjust the ultrafiltration volume for duration of dialysis session, which may have limited their findings. Our finding that higher UFR was associated with improved scores on Trails B at 1-year follow-up warrants further investigation to determine if this is a statistical finding or a true clinical association.

A possible explanation for the association between higher UFR and improvement on Trails B is that the higher ultrafiltration per session led to an increase in middle molecule clearance, which we did not measure in our study. Middle molecule clearance need further evaluation in cognitive function, especially as they are postulated to be neurotoxic.[1] Of note, Kt/V is more of a measure of small molecule clearance and was not associated with Trails B score in our study or previous literature.[24]

In contrast to our results, there is literature that suggests a role of intradialytic BP variability in cognitive impairment. In a study evaluating changes in cognitive performance from predialysis to postdialysis, the frequency of hypotensive episodes (SBP <90 or DBP <50) during dialysis was associated with decline in performance on tasks of attention.[25] However, it was not demonstrated whether the cognitive impairment noted after a dialysis session is a permanent versus a temporary effect. In a randomized trial evaluating intradialytic hemodynamic stress, investigators demonstrated that, over a 1-year period, persons dialyzed with cooled dialysate had better stability of mean arterial pressures during dialysis and no changes in brain white matter microstructure, whereas the control group exhibited increased variability in mean arterial pressures and a decrease in white matter integrity.[26] However, they did not report cognitive performance results, which have greater patient relevance.

The lack of overall cognitive decline over our 1-year study period also is surprising as a previous study noted a decrease in global cognitive score in a hemodialysis cohort over a 1-year period,[6] and there is strong evidence demonstrating the high prevalence of cognitive impairment in the HD population.[27] However, there is no clear evidence on the timing of cognitive decline in relationship to dialysis initiation. Literature demonstrates that the incidence of stroke is actually highest in the 2 months surrounding dialysis initiation, with incidence rates back to baseline at 1 year after initiation.[28] If cognitive impairment results from a

Table 4. Change in Test Scores (12 Month Score Minus Baseline Score) Associated With Change in Each SBP and UFR Variable

Cognitive Tests	Systolic Blood Pressure Measure	Rate of Change in Difference of Score[a] From Baseline to 12 Months	95% CI	*P*-value	Corrected *P*-value[b]
Montreal Cognitive Assessment (MoCA)	Change in blood pressure pre to post	-0.07	-0.71, 0.57	0.81	
	Maximum decrease in blood pressure	-0.15	-1.00, 0.70	0.71	
	Minimum blood pressure	-0.01	-0.80, 0.77	0.97	
	Ultrafiltration rate	0.01	-0.36, 0.38	0.95	
Hopkins Immediate	Change in blood pressure pre to post	1.25	-0.91, 3.42	0.25	
	Maximum decrease in blood pressure	0.66	-1.74, 3.05	0.58	
	Minimum blood pressure	-1.69	-3.62, 0.23	0.08	0.46
	Ultrafiltration rate	-0.24	-1.21, 0.73	0.62	
Hopkins Delayed	Change in blood pressure pre to post	-1.31	-3.35, 0.73	0.20	
	Maximum decrease in blood pressure	2.32	0.21, 4.43	0.03	0.30
	Minimum blood pressure	-0.45	-2.37, 1.47	0.63	
	Ultrafiltration rate	-0.28	-1.20, 0.64	0.54	
Hopkins Recognition	Change in blood pressure pre to post	2.75	-1.26, 6.77	0.17	
	Maximum decrease in blood pressure	-1.04	-5.54, 3.45	0.64	
	Minimum blood pressure	-2.46	-6.15, 1.22	0.18	
	Ultrafiltration rate	-0.04	-1.86, 1.79	0.97	
Trails A	Change in blood pressure pre to post	-0.19	-2.31, 1.93	0.86	
	Maximum decrease in blood pressure	-0.37	-2.69, 1.95	0.75	
	Minimum blood pressure	-0.67	-2.60, 1.27	0.49	
	Ultrafiltration rate	0.51	-0.41, 1.43	0.26	
Trails B	Change in blood pressure pre to post	-2.32	-4.92, 0.29	0.08	0.46
	Maximum decrease in blood pressure	1.55	-1.39, 4.49	0.29	
	Minimum blood pressure	0.06	-2.47, 2.59	0.96	
	Ultrafiltration rate	1.95	0.91, 3.00	<0.01	0.03
Controlled Oral Word Association Test (COWAT)	Change in blood pressure pre to post	1.05	-1.10, 3.21	0.33	
	Maximum decrease in blood pressure	-0.50	-2.87, 1.88	0.67	
	Minimum blood pressure	-1.33	-3.26, 0.60	0.17	
	Ultrafiltration rate	0.58	-0.43, 1.59	0.25	
Animal Naming	Change in blood pressure pre to post	0.36	-0.86, 1.58	0.55	
	Maximum decrease in blood pressure	0.00	-1.36, 1.37	1.00	
	Minimum blood pressure	-0.36	-1.49, 0.77	0.52	
	Ultrafiltration rate	0.26	-0.29, 0.82	0.34	
Digit Span	Change in blood pressure pre to post	-0.11	-0.67, 0.46	0.70	
	Maximum decrease in blood pressure	0.22	-0.39, 0.83	0.46	
	Minimum blood pressure	-0.55	-1.02, -0.08	0.02	0.30
	Ultrafiltration rate	0.06	-1.87, 3.06	0.62	

[a]Rate of change in score per 10 mmHg increment in systolic blood pressure measures and 1 ml/kg/h for ultrafiltration rate.
[b]Corrected *P*-value adjusts for false positive results present in multiple comparison testing.

mechanism similar to stroke (ie, reduced cerebral perfusion and ischemic injury),[29] then our use of prevalent patients with an average of 4.5 years on dialysis may not have been able to capture hemodynamic associated cognitive decline. Our evaluation of the 9 participants with less than 1 year of dialysis at enrollment did show a trend toward greater decline in cognitive test score compared to those who had been on dialysis for more than 1 year. We hypothesize that cognitive decline associated with intradialytic hemodynamic instability may occur early after dialysis initiation when patients are still adjusting to the dialysis process.

We acknowledge several limitations. First, small sample size (with only 32 participants completing the study) limits interpretation of our results, as we were not able to obtain our goal sample size of 43 participants. Additionally, the majority of participants in our small cohort were African American, which is in contrast to most literature in this field with predominantly white participants. Race is associated with performance on cognitive testing.[30] It is important to note that our cohort is representative of the Milwaukee-area dialysis population and demonstrates similar levels of cognitive impairment seen in other studies.[6,27] Second, we observed severe cognitive impairment at baseline with mean (SD) MoCA score of 21.8 (3.8). This may have limited our ability to detect further decline in performance due to floor effects as we did not note further decline over the 1-year period. Third,

with an average minimum intradialytic SBP of 112 mmHg, our cohort did not demonstrate a high degree of hypotension; thus our cohort may not have been at high risk for hypotensive-related ischemic brain injury as a cause of cognitive decline. Fourth, our use of changes in sphygmomanometer-measured BP may not have been adequate to detect hemodynamic instability. In the above-mentioned study that demonstrated an association between intradialytic hemodynamic stability and preserved brain white matter integrity, the investigators used a novel hemodynamic model that used beat-to-beat measurements and variability, which provides greater granularity of intradialytic hemodynamics compared to sphygmomanometer-measured BP changes. Finally, we did not obtain information on use of interventions to avoid hypotension such as saline infusion or dialysate cooling.

CONCLUSIONS

Our pilot study is the first longitudinal evaluation of cognitive changes in relation to intradialytic hemodynamics that included a comprehensive evaluation of intradialytic BPs, UFR, and cognitive domains. The contribution of dialysis to cognitive decline is an important area for research. Our study does not demonstrate that intradialytic BP fluctuations are associated with change in cognitive test scores in prevalent dialysis patients over a 1-year period. However, higher ultrafiltration rate was associated with improved executive functioning. The role of both hemodynamics and ultrafiltration in cognitive impairment needs further investigation in larger cohorts with a more sensitive measure of hemodynamics and cerebral perfusion. Such an association may be more apparent at the time dialysis is initiated, when cognitive changes may be more likely. This is an important area of focus as both intradialytic BPs and ultrafiltration rate are potentially modifiable through use of medications, changes in dialysate temperature, session duration, and dialysis modality.

Funding/Support: None declared.

Financial Disclosures: None declared.

REFERENCES

1. Murray AM. Cognitive impairment in the aging dialysis and chronic kidney disease populations: an occult burden. *Adv Chronic Kidney Dis*. 2008;15(2):123-132.

2. U.S. Renal Data System, USRDS 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2005.

3. Kurella M, Mapes DL, Port FK, Chertow GM. Correlates and outcomes of dementia among dialysis patients: the Dialysis Outcomes and Practice Patterns Study. *Nephrol Dial Transplant*. 2006;21(9):2543-2548.

4. Drew DA, Weiner DE, Tighiouart H, et al. Cognitive function and all-cause mortality in maintenance hemodialysis patients. *Am J Kidney Dis*. 2015;65(2):303-311.

5. Wolfgram DF, Szabo A, Murray AM, Whittle J. Risk of dementia in peritoneal dialysis patients compared to hemodialysis patients. *Perit Dial Int.* 2015;(2)189-198.

6. Bossola M, Antocicco M, Di Stasio E, et al. Mini Mental State Examination over time in chronic hemodialysis patients. *J Psychosom Res*. 2011;71(1):50-54.

7. Etgen T, Chonchol M, Förstl H, Sander D. Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis. *Am J Nephrol*. 2012;35(5):474-482.

8. Madero M, Sarnak MJ. Does hemodialysis hurt the brain? *Semin Dial*. 2011;24(3):266-268.

9. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. *Am J Kidney Dis.* 45:S1-S154, 2005 (suppl 3).

10. Davenport A. What are the causes of the ill effects of chronic hemodialysis? Balancing risks: blood pressure targets, intradialytic hypotension, and ischemic brain injury. *Semin Dial*. 2014;27(1):13-15.

11. Stefanidis I, Bach R, Mertens PR, et al. Influence of hemodialysis on the mean blood flow velocity in the middle cerebral artery. *Clin Nephrol.* 2005;64(2):129-137.

12. Drew DA, Bhadelia R, Tighiouart H, et al. Anatomic brain disease in hemodialysis patients: a cross-sectional study. *Am J Kidney Dis*. 2013;61(2):271-278.

13. Fazekas G, Fazekas F, Schmidt R, Kapeller P, Offenbacher H, Krejs GJ. Brain MRI findings and cognitive impairment in patients undergoing chronic hemodialysis treatment. *J Neurol Sci*. 1995;134(1-2):83-88.

14. Wolfgram DF, Sunio L, Vogt E, et al. Hemodynamics during dialysis and cognitive performance. *Nephrology (Carlton)*. 2014;19(12)771-776.

15. Pearson. Advanced clinical solutions for WAIS-IV and WMS-IV: Administration and scoring manual. San Antonio, TX: NCS Pearson, Inc; 2009.

16. Wechsler D. Wechsler Adult Intelligence Scale - Fourth Edition. San Antonio, TX:Pearson; 2008.

17. Heaton R, Miller, SW, Taylor MJ, Grant I. Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults. Lutz, FL: Psychological Assessment Resources, Inc; 2004.

18. Brandt J, Benedict R. Hopkins Verbal Learning Test-Revised. Professional manual. Lutz, FL: Psychological Assessment Resources, Inc; 2001.

19. Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS) Recent evidence and development of a shorter version. In: Brink TL, ed. *Clinical Gerontology: A Guide to Assessment and Intervention*. New York: The Haworth Press; 1986:165-173.

20. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360(9349):1903-1913.

21. Prohovnik I, Post J, Uribarri J, Lee H, Sandu O, Langhoff E. Cerebrovascular effects of hemodialysis in chronic kidney disease. *J Cereb Blood Flow Metab*. 2007;27(11):1861-1869.

22. Giang LM, Tighiouart H, Lou KV, et al. Measures of blood pressure and cognition in dialysis patients. *Hemodial Int*. 2013;17(1):24-31.

23. Kurella Tamura M, Larive B, Unruh ML, et al; Frequent Hemodialysis Network Trial Group. Prevalence and correlates of cognitive impairment in hemodialysis patients: the Frequent Hemodialysis Network trials. *Clin J Am Soc Nephrol*. 2010;5(8):1429-1438.

24. Kurella Tamura M, Unruh ML, Nissenson AR, et al; Frequent Hemodialysis Network Trial Group. Effect of more frequent hemodialysis on cognitive function in the frequent hemodialysis network trials. *Am J Kidney Dis*. 2013;61(12):228-237.

25. Costa AS, Tiffin-Richards FE, Holschbach B, et al. Clinical predictors of individual cognitive fluctuations in patients undergoing hemodialysis. *Am J Kidney Dis*. 2014;64(3):434-442.

26. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. *J Am Soc Nephrol.* 2014; 26(4):957-965.

27. Murray AM, Tupper DE, Knopman DS, et al. Cognitive impairment in hemodialysis patients is common. *Neurology*. 2006;67(2):216-223.

28. Murray AM, Seliger S, Lakshminarayan K, Herzog CA, Solid CA. Incidence of stroke before and after dialysis initiation in older patients. *J Am Soc Nephro*l. 2013;24(7):1166-1173.

29. Yoshimitsu T, Hirakata H, Fujii K, et al. Cerebral ischemia as a causative mechanism for rapid progression of brain atrophy in chronic hemodialysis patients. *Clin Nephrol.* 2000;53(6):445-451.

30. Tang MX, Cross P, Andrews H, et al. Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. *Neurology*. 2001;56(1):49-56.

Erythrocyte Sedimentation Rate and C-reactive Protein Measurements and Their Relevance in Clinical Medicine

Christopher Bray, MD, PhD; Lauren N. Bell, PhD; Hong Liang, PhD; Rasha Haykal, MD; Farah Kaiksow, MD; Joseph J. Mazza, MD; Steven H. Yale, MD

ABSTRACT

Introduction: Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are widely used laboratory markers of systemic inflammation.

Objective: A thorough understanding of the similarities and differences between these two serological markers, including factors that affect measurements, is necessary for the proper utilization and interpretation of ESR and CRP.

Methods: This review summarizes the current published literature (searched on MEDLINE through February 2016) surrounding the history and utilization of ESR and CRP, and examines factors that affect ESR and CRP measurements and discordance amongst these two inflammatory markers.

Results: As ESR and CRP lack sensitivity or specificity, these tests should be used only in combination with clinical history and physical exam for diagnosis and monitoring of pathological conditions. The clinical application of these tests in diagnosis is best applied to conditions in which there is high or low clinical probability of disease. Importantly, discrepancies between ESR and CRP measurements commonly have been reported in both inpatient and outpatient settings and this problem may be particularly prevalent in chronic inflammatory diseases. Numerous physiological factors, including noninfectious conditions and resolution of inflammation can contribute to abnormally high ESR/low CRP readings or vice versa.

Conclusions: Although discordance may be encountered in certain settings, proper utilization of ESR and CRP measurements continues to play an important role in clinical management of many inflammatory and other conditions.

BACKGROUND

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are two commonly ordered laboratory tests that may aid clinicians in accurately diagnosing and following many complex disease states. Although these tests have a low index of specificity and are influenced by numerous disease factors, they may provide the clinician with valuable information and additional focus when used in conjunction with other clinical and diagnostic data. ESR and CRP may be particularly important as a component of the rapid yet complex decision making that is required in individuals with multiple comorbidities and in the intensive care unit.

• • •

Author Affiliations: Internal Medicine Residency Program, North Florida Regional Medical Center, Gainesville, Fla (Bray, Bell, Liang, Haykal, Yale); Internal Medicine Residency Program, Tulane University, New Orleans, La (Kaiksow); Department of Clinical Research, Marshfield Clinic Research Foundation, Marshfield, Wis (Mazza).

Corresponding Author: Steven H. Yale, MD, Program Director, Internal Medicine Residency Program, Medical Arts Building 101B, 6500 Newberry Road, Gainesville, FL 32614; phone 352.313.4109; fax 352.333.4800; e-mail steven.yale@hcahealthcare.com.

DISCUSSION

Erythrocyte Sedimentation Rate

The ESR measures the rate at which erythrocytes fall or settle in the plasma of a randomly drawn anticoagulated blood specimen over a specified period of time (usually 60 minutes) in millimeters (mm)/hour; however, newer methods involving centrifugation can generate results in approximately 5 minutes.[1,2] This phenomenon was first observed in 1897 by Dr Edmund Faustyn Biernacki, who found that the rate at which blood settled varied among individuals and that red blood cells (RBCs) settled more quickly in the presence of increased levels of fibrinogen.[3] In 1918, Dr Robert Fahraeus noted that ESR differed in pregnant versus nonpregnant women and saw the test as a possible indicator of pregnancy.[3] In 1921, Dr Alf Vilhelm Albertsson Westergren used ESR as a laboratory indicator of the prognosis of patients with pulmonary tuberculosis.[4] Dr Westergren defined the measurement standards for the ESR test that still are used widely today, including utilization of sodium citrate as an anticoagulant.

The ESR can be confounded by many factors, leaving this widely used test vulnerable to misinterpretation in clinical practice.[5,6] Aggregation of erythrocytes promotes falling and increases the ESR; however, RBCs are negatively charged and tend to repel

Table 1. Conditions Associated With a Change in CRP and ESR

Conditions Associated With a Mild Rise in CRP	Conditions Associated With a Major Rise in CRP	Conditions Associated With a Mild Rise in ESR	Conditions Associated With a Major Rise in ESR
• Viral infections	• Active inflammation	• Increasing age	• Malignancy
• Late pregnancy	• Severe bacterial infection	• Female gender	• Temporal arteritis
	• Burns	• Pregnancy	• Renal disease
Mucosal Infections		• Anemia	• Collagen vascular diseases
• Periodontitis		• Red blood cell abnormalities (including macrocytosis)	
• Stomatitis			
• Sinusitis		**Technical factors:**	
• Baginitis		• Dilutional problem	
• Intestinal hyperpermeability		• Increased temperature of specimen	
• Bacterial translocation		• Tilted ESR tube	
Noninfectious Causes of Mild Inflammation		**Elevated fibrinogen level:**	
• Obesity		• Inflammation	
• Insulin resistance		• Infection	
• Pancreatitis		• Malignancy	
• Smoking		• Diabetes	
• Uremia		• Renal disease	
• Cardiac ischemia		• Heart disease	
• Oral hormone replacement therapy		• Collagen vascular diseases	
• Sleep disturbance			
• Chronic fatigue			
• Mild alcohol consumption			
• Depression			
• Increasing age			

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

one another. Thus, the presence of positively charged, large, asymmetric acute phase proteins such as fibrinogen and immunoglobulins increases the ESR. The rate of erythrocyte settlement can be influenced by a wide variety of immune and nonimmune factors, including alterations of the quality and quantity of the RBCs, as well as changes in the normal patterns and amounts of various plasma proteins. Anemia and polycythemia (primary and secondary) represent quantitative changes in erythrocytes in various clinical conditions and will increase and decrease the ESR, respectively. Similarly, hemoglobinopathies and conditions associated with altered erythrocytes such as sickle cell disease have a low sedimentation rate during sickle crises that increases in the presence of moderate to severe infections.[7,8] Significant alterations in the array of plasma proteins and their ratio to one another also can have a major effect on the ESR, such as with cytokine-induced elevations in acute-phase proteins in response to infection, inflammation, or trauma. As a result of various factors—both cellular and noncellular—that affect the sedimentation rate, it is difficult to determine a "normal" or reference range. However, normal ESR commonly is defined in men as age in years divided by 2 and for women, age in years plus 10.[9] The ESR is thus higher in women, particularly during menses and pregnancy.

Alterations in circulating levels of plasma proteins such as fibrinogen and immunoglobulins that are typically associated with systemic illnesses are known to influence ESR. These individual proteins may provide useful information with respect to the specific disease process causing an elevated ESR.[10] Due to the long half-life of some plasma proteins and perhaps a longer amplified response time, the ESR does not change rapidly at the beginning of the inflammatory process and normalizes more slowly than that of other acute phase reactants, an important point to consider when applying the results to clinical practice. As discussed later in this paper, the characteristics of these temporal changes may account for discrepancies identified between ESR and other acute phase reactants.

C-reactive Protein

CRP was discovered by Tillet and Francis in 1930 in patients with pneumococcal pneumonia, where it was found to interact with the C-polysaccharide of streptococcus pneumoniae cell wall, hence the term C-reactive protein.[11] Originally CRP was measured qualitatively using the Quelling reaction, which involved precipitation of C-polysaccharide in serum and gave a simple "positive" or "negative" response.[12] However, more precise methods of measurement (often expressed in mg/dl) that give results in approximately 15

to 30 minutes have been developed using light scattering from CRP-specific antibody aggregates. High-sensitivity assays also are commonly used to quantitate low levels of CRP.

CRP is a nonspecific acute phase reactant that is a member of the pentraxin proteins, which are pattern recognition proteins that are an integral part of the innate immune system. CRP is produced and synthesized in the liver in response to inflammatory cytokines and assists in complement binding and phagocytosis by macrophages. Thus, one of the major roles of CRP is the recognition and elimination of certain foreign pathogens, including endotoxemia.[13] CRP also may help with clearance of necrotic or apoptotic cells.[14] More generally, CRP is one of the many acute phase reactants that is elaborated in response to inflammation and/or tissue injury, and its rise is commensurate with inflammatory mediators (cytokines) produced by cells actively participating in the milieu of tissue injury such as IL-6, IL-1, TGF-β, and TNF-α.[15,16] The level of CRP tends to be proportional to the intensity of the inflammatory process, and levels of this marker are therefore sensitive to subtle changes in the acute-phase response.[15,17,18] Accordingly, levels of CRP fall quickly because of its short half-life (4 to 7 hours) once inflammation subsides.

When Is It Appropriate to Use ESR and CRP in Clinical Practice?

***Clinical application of ESR and CRP*—**The acute phase reactants ESR and CRP are used clinically for diagnosis and monitoring of inflammatory conditions such as infections, trauma, infarction, neoplasm, inflammatory arthritis, and systemic autoimmune disease (Table 1). However, because ESR and CRP lack sensitivity or specificity, they should not be used exclusively for diagnosis. Furthermore, a normal result should not necessarily dissuade one from a clinical diagnosis. For example, elevations in ESR may be diagnostic of temporal arteritis or polymyalgia rheumatica, although patients diagnosed with these conditions sometimes exhibit low or normal ESR.[19,20]

ESR and CRP levels also may provide insight into the underlying disease process. Elevations in ESR reflect disease states that involve increased plasma protein/fibrinogen levels such as autoimmune conditions or cardiovascular disease. Increased levels of CRP generally are reflective of underlying inflammation, such as that resulting from trauma or infection. In contrast, deceptively low CRP levels may be found in patients with infections caused by low virulence organisms or in those treated with antibiotics. In the case of functional disorders such as irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, and somatic symptom disorders, a normal ESR and CRP may help to distinguish these conditions from organic pathology.[21]

Although ESR and CRP have been utilized in combination to diagnose and monitor various conditions for many years, CRP is somewhat preferred as a serological marker for acute disease.[22] In acute inflammatory conditions, CRP can rise as much as 50 to 100 mg/L within 4 to 6 hours of a mild to moderately noxious stimulus, such as an uncomplicated skin infection, cystitis, or bronchitis. CRP levels double every 8 hours and peak 36 to 50 hours after the onset of inflammation or injury.[12] Mild increases in CRP between 2 mg/L and 10 mg/L are considered to be metabolic inflammation. Conversely, markedly elevated levels of CRP (>100-500 mg/L) are strongly associated with bacterial infections.[15] The ESR, in contrast, begins to rise within 24 to 48 hours of the onset of inflammation, decreases slowly as inflammation resolves, and can take weeks to completely normalize.[12,23] Importantly, investigation of underlying etiology should be carried out in patients with ESR values greater than 100 mm/hour as the positive predictive value for an identifiable cause of marked ESR elevation is 90%.[24] As CRP values tend to drop quickly with treatment, ESR has been proposed to be a better marker for clinical monitoring, following the course of disease over time, and predicting treatment response/duration for temporal arteritis, polymyalgia rheumatica, rheumatoid arthritis, and Hodgkin's disease.[25] CRP may be used to follow the course of disease and to monitor treatment effectiveness for bacterial infections, rheumatoid arthritis, malignancies, and acute pancreatitis. Similarly, serial measurement of CRP may be beneficial for predicting the occurrence of postoperative and neonatal sepsis.[26,27] ESR and CRP levels at admission also can be useful in predicting severity of soft-tissue infections and thus prolonged hospitalization or a poor response to treatment.

***Utilization of ESR and CRP for Medical Decision Making in Clinical Practice*—**As ESR and CRP lack sensitivity or specificity, for a patient with indeterminate clinical suspicion of disease, an ESR and/or CRP measurement does not alter disease probability sufficiently to change medical decision making and course of treatment. However, for a patient with low clinical suspicion of disease, a low ESR and/or CRP measurement may decrease the posttest probability to an even greater extent, giving the physician additional confidence in ruling out disease. A high ESR and/or CRP measurement in patients with low clinical suspicion of disease may prompt the physician to examine test conditions for errors and/or monitor ESR/CRP values over time. On the other hand, for a patient with high clinical suspicion of disease, a high ESR and/or CRP measurement may increase posttest probability to aid with identification of a definitive diagnosis, whereas a low ESR and/or CRP measurement does not change the clinician's disease suspicion enough to alter the course of treatment. A highly generalized bedside clinical approach for use of ESR and/or CRP tests based on these principles is summarized in the Figure.

Based on Bayes' rule and the generalized bedside clinical approach described above and in the Figure, an ESR/CRP test result can be used to aid medical decision making based on pre-

Figure. Utilization of ESR and/or CPR Tests to Aid in Clinical Decision Making

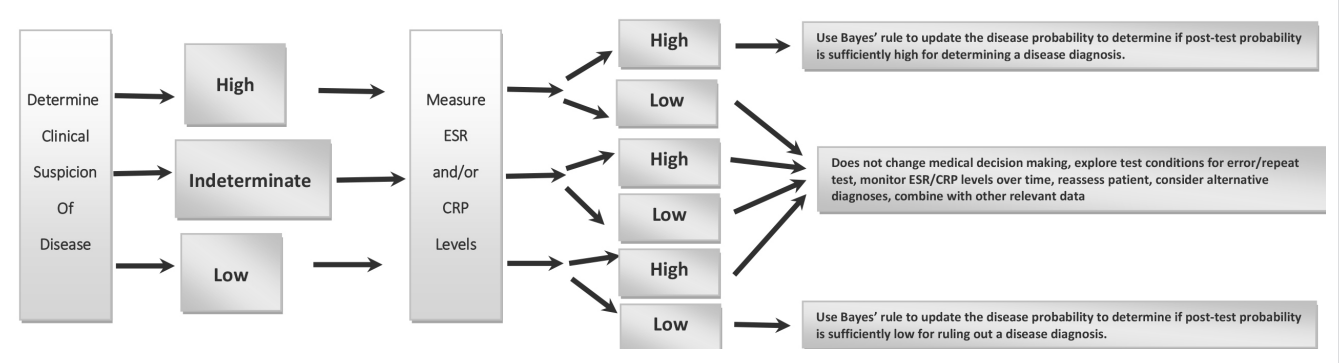


Table 2. Discordant Values in Hospitalized Patients

High ESR/Low CRP	High CRP/Low ESR
• Infections (Bone and joint)	• Infections (urinary tract, gastrointestinal tract, lung and bloodstream)
• Connective tissue disease (SLE)	• Myocardial infarction
• Ischemic stroke	• Venothromboembolic disease
• Malignancy	• Rheumatoid arthritis
• Renal insufficiency	• Low serum albumin
• Low serum albumin	

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SLE, systemic lupus erythematosus.

test versus posttest disease probability. For example, in a study by Hopstaken et al, the pretest probability (prevalence) of pneumonia among patients with lower respiratory tract infections was 13%. At an ESR cut-point of ≥10 mm/hour, the sensitivity was 97% and specificity 28% for diagnosing pneumonia.[28] Applying Bayes' rule, the posttest probability of pneumonia in a patient with an ESR measurement <10 mm/hour dropped to 1.6% while the posttest probability of pneumonia in a patient with an ESR measurement ≥10 mm/hour increased to 16.8%.

In another example based on a study by Falk et al, the pretest probability (prevalence) of community-acquired pneumonia (CAP) was 14.6%. At a CRP cut-point of ≤20 mg/L, the positive likelihood ratio was 2.1 and negative likelihood ratio 0.33, with a pretest probability of a patient having CAP of 14.6%.[29] Applying Bayes' rule in a patient with a CRP measurement ≤20 mg/L, the posttest probability of CAP dropped to 5.3%, while the posttest probability of having CAP with a CRP measurement >20 mg/L increased to 26.5%.

How Should Discordant ESR and CRP Measurements Be Managed?

ESR, CRP, and other positive acute phase reactants generally rise in tandem with inflammation. However, this is not seen uniformly among all patients. In chronic inflammatory conditions, the accuracy and sensitivity of ESR and CRP has been a topic of debate. For example, in infections or malignant neoplasms, ESR has been found to have low sensitivity but high specificity. Similarly, CRP is synthesized in the liver, and hepatic failure has been reported to markedly impair CRP production in the setting of overwhelming sepsis.[30]

Previous studies have reported up to a 12% discordance rate (approximately 1 in 8 patients) between ESR and CRP values in hospitalized patients.[16,31] Examples of conditions in which a high ESR/low CRP or high CRP/low ESR may be observed are summarized in Table 2. This frequent discordance between ESR and CRP may be attributable to various factors, including differences in cytokine stimulation, inherent differences in normalization, or false positive/false negative characteristics of individual acute phase reactants. In addition, it is important to consider age, gender, and adiposity, as ESR increases with age in healthy subjects, high ESR/low CRP discordance tends to be observed in women (likely due to their propensity to develop connective tissue disorders), and CRP levels generally increase in overweight and obese individuals.[5,32]

Although correlation coefficients between ESR and CRP measurements may be statistically significant across cohorts,[22,31] many patients exhibit conflicting results. Discordant values seen in various disease states may be caused by (1) resolution of recent inflammation, (2) presence of increased globulins such as in IgG4-related disease, Waldenstrom's macroglobulinemia and multiple myeloma (normal-mild-moderate CRP/elevated ESR), (3) medical conditions interfering with CRP such as connective tissue disease and stroke (low-normal CRP/elevated ESR), or (4) lack of sensitivity of ESR in the setting of known inflammation as in mucosal infections, myocardial infraction, venothromboembolism, renal disease, and disturbances in serum albumin (elevated CRP/low-normal ESR). For example, in systemic lupus erythematosus (SLE), ESR is often elevated—sometimes markedly—while the CRP response shows a less robust elevation, possibly related to interferon suppression of CRP production. In patients with giant cell arteritis, taking statin and nonsteroidal antiinflammatory medications was associated with a lower ESR.[33] Discordance of ESR and CRP in patients with rheumatoid arthritis has been

attributed to differences in inflammatory response timing, with a rapid rise in CRP coupled to a slower increase in ESR.[34]

CONCLUSION

ESR and CRP can aide the physician in the diagnostic algorithm and clinical monitoring of various infectious or inflammatory conditions. Because of the limitations of ESR and CRP described above, these tests are more useful in confirming a provider's clinical suspicion for an inflammatory or infectious process rather than generating a specific diagnosis or initiating a protocol-driven treatment plan. Clinicians should be aware of the limitations of these tests and the conditions that may account for discordant results and utilize them within the clinical context in which they are obtained.

Funding/Support: None declared.

Disclosure: Christopher Bray, Lauren N. Bell, Hong Liang, and Steven H. Yale are employees of North Florida Regional Medical Center/Hospital Corporation of America.

REFERENCES

1. Batlivala SP. Focus on diagnosis: the erythrocyte sedimentation rate and the C-reactive protein test. *Pediatr Rev*. 2009;30(2):72-74.

2. Janson L, Tischler M. T*he Big Picture: Medical Biochemistry*. New York, NY: McGraw-Hill; 2012.

3. Grzybowski A, Sak JJ. Who discovered the erythrocyte sedimentation rate? J *Rheumatol.* 2011;38(7):1521-1522; author reply 1523.

4. Westergren A. The technique of the red cell sedimentation rate. *Am Rev Tuber.* 1926;14:94-101.

5. Colombet I, Pouchot J, Kronz V, et al. Agreement between erythrocyte sedimentation rate and C-reactive protein in hospital practice. *Am J Med*. 2010;123(9):863.e7-13.

6. Jurado RL. Why shouldn't we determine the erythrocyte sedimentation rate? *Clin Infect Dis*. 2001;33(4):548-549.

7. Olshaker JS, Jerrard DA. The erythrocyte sedimentation rate. J Emerg Med. 1997;15(6):869-874.

8. Ahmed YF, Abbag FI, Al-Qahtani JM, Ghazali BM, Abolfotouh MA. Erythrocyte sedimentation rate during steady state, painful crisis and infection in children with sickle cell disease. *Saudi Med J.* 2000;21(5):461-463.

9. Miller A, Green M, Robinson D. Simple rule for calculating normal erythrocyte sedimentation rate. *Br Med J* (Clin Res Ed). 1983;286(6361):266.

10. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J M*ed. 1999;340(6):448-454.

11. Tillett WS, Francis T Jr. Serological Reactions in Pneumonia with a Non-Protein Somatic Fraction of Pneumococcus. *J Exp Med*. 1930;52(4):561-571.

12. Litao MK, Kamat D. Erythrocyte sedimentation rate and C-reactive protein: how best to use them in clinical practice. *Pediatr Ann*. 2014;43(10):417-420.

13. Xia D, Samols D. Transgenic mice expressing rabbit C-reactive protein are resistant to endotoxemia. *Proc Natl Acad Sci USA*. 1997;94(6):2575-2580.

14. Gershov D, Kim S, Brot N, Elkon KB. C-Reactive protein binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an antiinflammatory innate immune response: implications for systemic autoimmunity. *J Exp Med*. 2000;192(9):1353-1364.

15. Markanday A. Acute Phase Reactants in Infections: Evidence-Based Review and a Guide for Clinicians. *Open Forum Infect Di*s. 2015;2(3):ofv098.

16. Costenbader KH, Chibnik LB, Schur PH. Discordance between erythrocyte sedimentation rate and C-reactive protein measurements: clinical significance. *Clin Exp Rheumatol*. 2007;25(5):746-749.

17. Dowton SB, Colten HR. Acute phase reactants in inflammation and infection. *Semin Hematol*. 1988;25(2):84-90.

18. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest*. 2003;111(12):1805-1812.

19. Helfgott SM, Kieval RI. Polymyalgia rheumatica in patients with a normal erythrocyte sedimentation rate. *Arthritis Rheum*. 1996;39(2):304-307.

20. Martinez-Taboada VM, Blanco R, Armona J, et al. Giant cell arteritis with an erythrocyte sedimentation rate lower than 50. *Clin Rheumatol*. 2000;19(1):73-75.

21. Katz PR, Gutman SI, Richman G, Karuza J, Bartholomew WR, Baum J. Erythrocyte sedimentation rate and C-reactive protein compared in the elderly. *Clin Chem*. 1989;35(3):466-468.

22. Keenan RT, Swearingen CJ, Yazici Y. Erythrocyte sedimentation rate and C-reactive protein levels are poorly correlated with clinical measures of disease activity in rheumatoid arthritis, systemic lupus erythematosus and osteoarthritis patients. *Clin Exp Rheumatol*. 2008;26(5):814-819.

23. Shusterman N, Kimmel PL, Kiechle FL, Williams S, Morrison G, Singer I. Factors influencing erythrocyte sedimentation in patients with chronic renal failure. *Arch Intern Med*. 1985;145(10):1796-1799.

24. Fincher RM, Page MI. Clinical significance of extreme elevation of the erythrocyte sedimentation rate. *Arch Intern M*ed. 1986;146(8):1581-1583.

25. Brigden ML. Clinical utility of the erythrocyte sedimentation rate. *Am Fam Physician*. 1999;60(5):1443-1450.

26. Benitz WE, Han MY, Madan A, Ramachandra P. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. *Pediatrics*. 1998;102(4):E41.

27. Mustard RA, Jr., Bohnen JM, Haseeb S, Kasina R. C-reactive protein levels predict postoperative septic complications. *Arch Surg*. 1987;122(1):69-73.

28. Hopstaken RM, Muris JW, Knottnerus JA, Kester AD, Rinkens PE, Dinant GJ. Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection. *Br J Gen Pract*. 2003;53(490):358-364.

29. Falk G, Fahey T. C-reactive protein and community-acquired pneumonia in ambulatory care: systematic review of diagnostic accuracy studies. *Fam Pract*. 2009;26(1):10-21.

30. Silvestre JP, Coelho LM, Póvoa PM. Impact of fulminant hepatic failure in C-reactive protein? *J Crit Care*. 2010;25(4):657.e7-12.

31. Feldman M, Aziz B, Kang GN, Opondo MA, Belz RK, Sellers C. C-reactive protein and erythrocyte sedimentation rate discordance: frequency and causes in adults. T*ransl Res*. 2013;161(1):37-43.

32. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA*. 1999;282(22):2131-2135.

33. Hegg R, Lee AG, Tagg NT, Zimmerman MB. Statin or nonsteroidal anti-inflammatory drug use is associated with lower erythrocyte sedimentation rate in patients with giant cell arteritis. *J Neuroophthalmol.* 2011;31(2):135-138.

34. Wolfe F. Comparative usefulness of C-reactive protein and erythrocyte sedimentation rate in patients with rheumatoid arthritis. *J Rheumatol.* 1997;24(8):1477-1485.

Training in Urban Medicine and Public Health: Preparing Physicians to Address Urban Health Care Needs

Cynthia Haq, MD; Melissa Lemke, MA; Michelle Buelow, MD, MPH; Marjorie Stearns, MPH; Christine Ripp, MD; Patrick McBride, MD, MPH

ABSTRACT

Background: Wisconsin is facing significant physician shortages. The University of Wisconsin School of Medicine and Public Health (UWSMPH) launched Training in Urban Medicine and Public Health (TRIUMPH) to recruit and prepare medical students to serve people living within urban Health Professional Shortage Areas.

Methods: Students are selected based on their commitment to improve health equity for urban populations. They complete clinical rotations, core curriculum, and community projects in Milwaukee, Wisconsin.

Results: Full program graduates are more likely to match into residencies serving the urban poor (50/50, 100%) and pursue primary care specialties (40/50, 80.0%) compared to nonprogram graduates.

Discussion: The TRIUMPH program has been successful in its mission to encourage graduates to serve urban communities. The authors discuss urban health disparities, TRIUMPH outcomes, and the need for similar programs.

BACKGROUND

Wisconsin is facing significant physician shortages,[1] and the need for primary care physicians continues to grow. The Robert Graham Center projects that by 2030 Wisconsin will need an additional 742 primary care physicians, as well as other physician specialists to adequately meet the needs of the state's growing population.[2] These shortages are exacerbated by an aging population and increasing needs for primary care physicians due to expanded health insurance coverage by the Afforadable Care Act.[3]

Many Wisconsin counties are designated as Health Professional Shortage Areas (HPSAs). This status is conferred by the US Health Resources and Services Administration to designate service areas, populations, or facilities with shortages of human resources to provide essential primary health care services.[4] In early 2016 there were 126 primary care HPSAs in Wisconsin; 27 were designated as metro, 73 as nonmetro, 2 as frontier, and 23 were individual clinics serving rural populations (1 was undesignated). While just 27/103 (26.2%) of Wisconsin HPSAs are designated as metro, due to the greater density of urban populations, 44% of people living in Wisconsin HPSAs (439,726 individuals in 2016) are urban medically underserved populations (MUPs).

Physician shortages are noticeable even in Milwaukee, Wisconsin's largest city, where an additional 57 primary care physicians would have been required to meet minimal thresholds for primary care physician coverage in 2013.[5] Innovative strategies are needed to address physician shortages for urban medically underserved populations. This report describes promising early outcomes of Training in Urban Medicine and Public Health (TRIUMPH), the University of Wisconsin School of Medicine and Public Health medical education program designed to recruit, train, and retain physicians to work with urban MUPs.

METHODS

The University of Wisconsin School of Medicine and Public Health (UWSMPH), as an integrated school of medicine and public health, is dedicated to promoting health and health equity. Faculty and staff collaborate with statewide partners to design programs to reduce health disparities and to conduct research to measure the health status of populations.[3] Additionally, the school offers educational programs to address the needs of

• • •

Author Affiliations: Department of Family Medicine and Community Health, University of Wisconsin- Madison School of Medicine and Public Health (UWSMPH), Madison, Wis (Haq, Lemke, Buelow, Stearns); Center for Urban Population Health, UWSMPH (Lemke); Sixteenth Street Community Health Centers, Milwaukee, Wis (Buelow); TRIUMPH graduate, UWSMPH; Family Medicine Resident, United Family Medicine, St. Paul, Minn (Ripp); Departments of Medicine, Family Medicine and Community Health, UWSMPH (McBride).

Corresponding Author: Cynthia Haq, MD, Professor of Family Medicine, University of Wisconsin School of Medicine and Public Health, 4260 Health Sciences Learning Center, 750 Highland Ave, Madison, WI 53705; phone 608.206.3527; fax 608.262.2327; e-mail cindy.haq@wisc.edu.

rural (Wisconsin Academy of Rural Medicine [WARM]), Native American (Native American Center for Health Professions), and remote populations (Global Health Institute).

Urban Health Track

TRIUMPH was designed to recruit and prepare medical students for careers to promote health and health equity for urban MUPs. The details of the curriculum and structure of TRIUMPH were outlined in a previous publication.[6] Students relocate from Madison to live and learn in diverse Milwaukee communities for the third and fourth years of medical school. TRIUMPH provides a core curriculum, clerkships, and community and public health experiences for 16 third-year (M3) and 16 fourth-year (M4) medical students per year. Clinical, community and public health, leadership, and self-care skills are taught in an integrated fashion (Figure, Table 1). Each of these domains is linked to specific teaching methods, educational objectives, and competencies (available on request). The required M4 preceptorship is completed as a longitudinal experience in the student's specialty of choice and, whenever possible, in Federally Qualified Health Centers.

Students meet weekly in small groups and through intensive courses to complete the core curriculum. Community leaders, neighborhood residents, and local health professionals provide students with background on the historic, socioeconomic, and cultural determinants of health. Students reflect on their experiences, receive and provide peer support, and enhance their skills to promote resilience and compassion through case-based discussions and humanism rounds with faculty leaders.

Community and Institutional Partners

TRIUMPH is comprised of a rich network of community and institutional partners. The UWSMPH provides leadership and infrastructure. Aurora Health Care provides clinical training sites. Motivated physicians, health professionals, and community leaders serve as teachers. Community-based physicians and staff of Federally Qualified Health Centers serve as committed role models working within urban HPSAs. Community organizations partner with TRIUMPH by proposing health-related projects that would benefit from the contributions of medical students (80 hours/year). The state legislature provides financial support and reviews outcomes annually to ensure that the program is addressing state needs.

Selection of Students

Medical student applicants undergo a rigorous selection process that includes personal essays, letters of recommendation, curriculum vitae, and interviews. The selection committee is comprised of faculty, community leaders, and M4 TRIUMPH students. Students are selected based on their commitment to improve health equity for urban populations, their leadership potential, and their ability to handle the additional demands of TRIUMPH.

Figure. TRIUMPH Currriculum Framework[a]

[a]Adapted from: Strelnick et al. The residency program in social medicine of Montefiore Medical Center: 37 years of mission-driven, interdisciplinary training in primary care, population health and social medicine. *Acad Med*. 2008;83:378-389; and Pathman DE, Steiner BD, Williams E, Riggins T. The four community dimensions of primary care practice. *J Fam Pract*. 1998;46:293-303.

Program Growth and Changes

TRIUMPH was launched in 2009 as a third-year (M3), 6-month program with a pilot group of 6 medical students. Interest among students has grown steadily to attract students from Wisconsin and beyond, and community partners have eagerly welcomed students. TRIUMPH has expanded 3 times in response to student and community interest—first in 2010 when a 9-month M4 component was added, in 2011 when an abbreviated M3-only program was added, and again in 2014, when funding became available to replace the abbreviated program by doubling from 8 to 16 the number of students accepted per year into the M3/M4 program.

RESULTS

Since it was launched, 102 M3 students have enrolled in TRIUMPH. From 2010 to 2016, seven annual cohorts—a total of 69 students—have participated in the M3/M4 or full version of TRIUMPH; 50 have graduated. All of the full TRIUMPH program graduates to date have entered residencies that emphasize service to people living in urban low-income communities. Across the 6 full TRIUMPH cohorts that have graduated, 40/50 (80.0%) students have entered residencies in primary care specialties, a percentage twice that of the 40.2% of the UWSMPH's graduates not enrolled in either TRIUMPH or WARM over the

Table 1. TRIUMPH Skills Framework

Domain/Skills
Personal and Leadership
• Explore humanistic values
• Share self-reflections, discoveries, and challenges
• Discuss critical events
• Enhance cultural awareness
• Develop healthy coping strategies
• Enhance networking skills
• Receive and provide peer support
• Develop self-confidence
• Clarify personal values and career goals
• Promote health equity and social justice
Clinical
• Provide patient-centered, compassionate care to patients from disadvantaged urban backgrounds
• Recognize and respond to social determinants of health
• Advocate to improve outcomes and reduce health disparities
• Access and enhance social and community resources
• Assist patients to navigate complex health systems
Community/Public Health
• Explore Milwaukee history, neighborhoods, social determinants
• Become familiar with local health care systems and financing
• Access public health data to identify and track disparities
• Identify community health assets
• Select priorities, strategies to improve health outcomes
• Deliver evidence-based community health promotion
• Collaborate with community leaders and organizations
• Cultivate relationships with colleagues and mentors
Integration/Application to Become Community-Engaged Physicians
• Model cultural humility and sensitivity
• Integrate personal, leadership, community, public health, and clinical skills
• Engage with communities to promote the health of a defined population
• Demonstrate leadership and advocacy skills to reduce health disparities
• Collaborate with interdisciplinary teams to improve health

Abbreviations: TRIUMPH, Training in Urban Medicine and Public Health.

Table 2. TRIUMPH Graduate Outcomes, 2010-2016

	Female	Primary Care Specialty	Wisconsin Residency	Wisconsin Home State
15-month TRIUMPH graduates (N=50)	62.0% (31)	80.0% (40)	32.0% (16)	66.0% (33)
6-month TRIUMPH graduates (N=31)	77.4% (24)	41.9% (13)	19.4% (6)	83.8% (26)
UWSMPH graduates[a] 2010-2016 (N=Varies)	9.3% (435) (N=882)	40.2% (361) (N=897)	30.4% (271) (N=892)	77.0% (621) (N=806)

[a]Graduates not enrolled in TRIUMPH or the Wisconsin Academy of Rural Medicine.
Abbreviations: TRIUMPH, Training in Urban Medicine and Public Health; UWSMPH, University of Wisconsin School of Medicine and Public Health.

Table 3. TRIUMPH Graduate Specialties[a]

	15-month TRIUMPH graduates N=50	6-month TRIUMPH graduates N=31
Emergency Medicine[a]	12.0% (6)	19.4% (6)
Family Medicine	42.0% (21)	16.1% (5)
General Surgery[a]	---	19.4% (6)
Internal Medicine	14.0% (7)	12.9% (4)
Internal Medicine/Dermatology[a]	---	3.2% (1)
Internal Medicine/Pediatrics	4.0% (2)	3.2% (1)
Internal Medicine/Primary Care Track	4.0% (2)	---
OB/GYN[a]	4.0% (2)	9.6% (3)
Ophthalmology[a]	---	3.2% (1)
Otolaryngology[a]	---	3.2% (1)
Pediatrics	14.0% (7)	9.6% (3)
Pediatrics/Psychiatry	2.0% (1)	---
Psychiatry[a]	4.0% (2)	---

[a]Nonprimary care specialties.
Abbreviations: TRIUMPH, Training in Urban Medicine and Public Health.

same time frame (2010-2016, Table 2). Nine full program graduates (18%) have completed Master of Public Health degrees. Graduates also have selected nonprimary care specialties critical to meet the needs of urban MUPs (Table 3).

Sixteen (32.0%) TRIUMPH graduates have remained in Wisconsin for residency training, including 6 at Aurora Family Medicine, 5 at the Medical College of Wisconsin, and 5 at UW-Madison. This is similar to the rate of UWSMPH's regular medical students graduating during 2010-2016 who remained in Wisconsin for their residency training (30.4%).

All of the 12 alumni who graduated from the full program and who had completed residencies will be/are practicing in urban areas, with 7 remaining in and/or moving back to Milwaukee. Seven will practice in clinics and hospitals that serve populations with at least 50% of people living in poverty; many others plan to return to practice in Milwaukee long-term.

DISCUSSION

TRIUMPH has been successful in recruiting, training and retaining physicians to work with urban MUPs. Participants have been more likely to enter primary care careers as compared to non-TRIUMPH and non-WARM students. Early outcomes confirm graduates are pursuing careers working with urban MUPs beyond residency graduation.

Several medical schools have developed initiatives to prepare students to work with urban underserved populations.[7] Health professionals working in HPSAs face unique challenges that increase their risk of burnout, thereby increasing physician turnover in areas of greatest need.[8-10] TRIUMPH is one of many innovative programs supported by UWSMPH to recruit and retain physicians to practice in these shortage areas.

TRIUMPH has grown and thrived due to several essential ingredients: UWSMPH, Aurora, and Milwaukee champions; motivated and capable students; experienced and receptive com-

munity partners; and state government support. Community partners have welcomed students and provided them with mentoring and real-life learning experiences. Community organizations have reported numerous benefits; each year they propose more projects than the number of students enrolled.[6]

TRIUMPH is 1 piece of a complex puzzle to address burgeoning health professional shortages and health disparities in urban communities. These outcomes confirm that with support, students can successfully complete medical school requirements as they are integrated into urban health systems, learn from and contribute to community organizations, and maintain their motivation to work with urban MUPs.

Our outcomes are limited by the lack of a control group and the fact that students who are selected for TRIUMPH demonstrate preexisting motivation to work with MUPs. Therefore, it is likely that many of these students may have pursued such career goals without participation in the program.

Early outcomes confirm that TRIUMPH has been successful in recruiting and preparing medical students to work with urban MUPs. Programs that prepare physicians to integrate community and public health, address the social determinants of health, and promote leadership, resilience and advocacy skills, should be bolstered and used to recruit and retain physicians to work in areas of greatest need. We encourage development of similar programs to strengthen the capacity of the health care workforce to serve people living in HPSAs in Wisconsin and beyond.

Acknowledgements: TRIUMPH is generously funded by the UWSMPH and by the state of Wisconsin. The authors are grateful to UWSMPH and Aurora faculty and staff, TRIUMPH coordinator Kathy Musack, Julie Foertsch and Raquel Borges-Garcia for evaluation and outcomes data, and Mindy Smith for her input on the manuscript.

TRIUMPH students have contributed creative ideas and shaped the evolution of the program. The people of Milwaukee and many community organizations and partners have generously opened their doors and hearts to TRIUMPH students. These partners include Aurora Family Service, Aurora School-Based Health Program - South Division High School, Aurora Health Center Midtown, Aurora St. Luke's Family Practice, Aurora UW Medical Group, Bread of Healing Clinic, Center for Urban Population Health, Children's Health Alliance of Wisconsin, City of Milwaukee Health Department, Community Advocates, Diverse and Resilient, Fondy Food Center, Growing Power, Keenan Central Health Clinic (City of Milwaukee Health Department), Lifecourse Initiative for Healthy Families, Lovell Johnson Quality of Life Center, Milwaukee Academy of Science/Aurora School-Based Health, Milwaukee Area Health Education Center (MAHEC), Milwaukee Center for Independence, Milwaukee County Breastfeeding Coalition, Milwaukee Health Care Partnership, Milwaukee Homicide Review Commission, Milwaukee Health Services (MLK Heritage Health Clinic), North Division High School (Milwaukee Public Schools), Penfield Children's Center, Sixteenth Street Community Health Centers, Outreach Community Health Ceter, Progressive Community Health Center, Southeastern Oneida Tribal Services, United Community Center, United Way of Greater Milwaukee and Waukesha County, Walker's Point Community Clinic-Aurora, Walnut Way Conservation Corp, Wisconsin WISEWOMAN, and the Zilber Family Foundation.

Funding/Support: None Declared.

Financial Disclosures: None Declared.

REFERENCES

1. Sugden NA, Udalova V, Walsh T. Wisconsin Physician Workforce Report. https://www.ahec.wisc.edu/documents/2012WIPhysicianWorkforceReport-8-18-14update.pdf. Published October, 2012. Updated December 28, 2012. Accessed November 29, 2016.

2. Petterson SM, Cai A, Moore M, Bazemore A. State-level projections of primary care workforce, 2010-2030. September 2013. Robert Graham Center, Washington D.C. http://www.graham-center.org/content/dam/rgc/documents/maps-data-tools/state-collections/workforce-projections/Wisconsin.pdf. Accessed November 29, 2016.

3. Greer DM, Baumgarder DJ, Bridgewater FD, et al. *Milwaukee Health Report 2013: Health Disparities in Milwaukee by Socioeconomic Status*. Milwaukee, WI: Center for Urban Population Health; 2013. http://www.cuph.org/uploads/2/5/8/0/25803255/mhr_2013_final.pdf. Accessed December 28, 2015.

4. Shortage Areas. Health Resources and Services Administration Data Warehouse website. http://datawarehouse.hrsa.gov/topics/shortageAreas.aspx. Accessed November 29, 2016.

5. Wisconsin Department of Health Services. Number of Primary Care Physician FTEs Needed to Remove Shortages for the Resident Population. https://www.dhs.wisconsin.gov/publications/p0/p00460.pdf. Published February 2013. Accessed November 29, 2016.

6. Haq C, Stearns M, Brill J, et al. Training in Urban Medicine and Public Health: TRIUMPH. *Acad Med*. 2013; 88(3): 352-363.

7. Girotti JA, Loy GL, Michel JL, Henderson VA. The Urban Medicine Program: Developing Physician-Leaders to Serve Underserved Urban Communities. *Acad Med*. 2015; 90(12): 1658-1666.

8. Shtasel D, Hobbs-Knutson K, Tolpin H, Weinstein D, Gottlieb GL. Developing a Pipeline for the Community-Based Primary Care Workforce and Its Leadership: The Kraft Center for Community Health Leadership's Fellowship and Practitioner Programs. *Acad Med*. 2015; 90(9): 1272-1277.

9. Bodenheimer T, Pham HH. Primary care: current problems and proposed solutions. *Health Aff* (Millwood). 2010; 29(5):799–805.

10. Committee on the Governance and Financing of Graduate Medical Education, Board of Health Care Services, Institute of Medicine. In: Eden J, Berwick D, Wilensky G, eds. Graduate Medical Education That Meets the Nation's Health Needs. Washington, DC: National Academies Press; 2014. https://www.ncbi.nlm.nih.gov/books/NBK248027/. Accessed Dec 10, 2016.

Is Central Pontine Myelinolysis Reversible?

David Lee Rebedew, MD

ABSTRACT

Central pontine myelinolysis (CPM) is a rare phenomenon that causes significant morbidity and mortality. Active therapeutic interventions for CPM can have a positive impact on recovery and overall prognosis. This case represents a 34-year-old white man with a chronic history of alcohol abuse who had Parkinsonian symptoms 13 days after rapid correction of his serum sodium in the hospital. Similarly to prior CPM case reports, this patient significantly improved following reinduction of hyponatremia, methylprednisolone, and/or plasmapharesis. This report demonstrates that CPM is potentially reversible when quickly recognized and therapeutic interventions are initiated rapidly.

CASE PRESENTATION

A 34-year-old white man with chronic alcohol abuse came into clinic for follow-up of his hospitalization for alcohol intoxication, hyponatremia, hypokalemia, and hypophosphatemia. Upon admission he had altered mental status with slurred speech in the setting of drinking 15 beers per day for the last 3 weeks and an otherwise normal physical exam. His initial sodium and potassium were 109 and 1.5, respectively. During the first 6 hours of his hospitalization, the sodium corrected to 119 with normal saline. Throughout the hospitalization, his mental status improved. He was discharged at his baseline mental status 4 days later.

Beginning 3 days after his discharge from the hospital, the patient noted new onset numbness in his legs and an unstable gait. Over the next few days, he had worsening jaw tremors, slurred speech, and difficulty swallowing. On review of systems, he had blurred vision in his left eye but denied fever, chills, night sweats, weight loss, bowel or bladder dysfunction, headache, or recent gastrointestinal/upper respiratory illness. He denied alcohol or other drug use since his hospital admission. On physical exam the patient had vertical nystagmus; bradykinesia; a slow, wide-based, unsteady, shuffling gait; a resting, pill-rolling tremor; as well as diffuse coarse tremors in his jaw, mouth, tongue, and legs. Cranial nerves II-XII were intact with 2+ biceps, brachioradialis, Achilles, and patellar reflexes bilaterally. Rapid alternating movements, Romberg sign, and finger-to-nose testing were within normal limits. He had muscle rigidity with passive range of motion, 5/5 strength except for 4/5 strength in his right hip flexor, and normal sensation to light touch, temperature, and pinprick throughout. Further neurological testing was negative for pronator drift, clonus, and asterixis. A basic metabolic panel was within normal limits. Urine and serum drug screens were negative. Magnetic resonance imaging (MRI) of the brain demonstrated a well-defined central pons lesion with a low T1 signal intensity on the sagittal view and high T2 signal intensity on an axial view consistent with central pontine myelinolysis (CPM) (see Figure).

In an attempt to reverse osmotic demyelination syndrome (ODS), induction of hyponatremia was initiated first. The serum sodium was lowered carefully, maintained, and slowly increased over the course of 6 days using a combination of minocycline, hypotonic saline, furosemide, desmopressin, and albumin. Serum sodium was maintained between the following sodium goals as noted: 122-125 mEq/L on days 1 and 2, 125-128 mEq/L on day 3, 128-132 mEq/L on days 4 and 5, and 132-135 mEq/L on day 6. Methylprednisolone was initiated simultaneously with the induction of hyponatremia.

The following day he was transferred to the intensive care unit (ICU) and intubated given concerns of inability to manage his secretions and airway. The patient subsequently required an intermittent norepinephrine drip to maintain his blood pressure.

Plasmapheresis was initiated on hospital day 3; the patient

• • •

Author Affiliations: Medical College of Wisconsin Affiliated Hospitals, Waukesha Family Practice Residency Program, University of Wisconsin School of Medicine and Public Health, Monroe Clinic.

Corresponding Author: David Lee Rebedew, MD, W6153 Tucker Rd, Monticello, WI 53570; phone 920.960.9953; fax 262.548.6903; e-mail david.lee.rebedew@gmail.com.

received 3 sessions in total. On hospital day 4, plasmapheresis was followed by intravenous immunoglobulin (IVIg). The next day he was extubated, then transferred out of the ICU 3 days later. Over the next 3 days, the patient's orientation improved from alert & oriented times 1 (A&Ox1) to A&Ox3, speech progressed from 25% to 100% intelligible, and clonus decreased from more than 50 beats to 8 beats bilaterally. Subsequently, he was transferred out of the ICU and discharged home 3 days later, performing all of his activities of daily living. One month later at an outpatient follow-up, the patient had no appreciable neurological deficits.

DISCUSSION

Central pontine myelinolysis, a subset of ODS, was first described in 1959 (coinciding with the introduction of plastic tubing and widespread use of IV fluid therapy) by Adams and Victor. ODS has been cited to account for 0.06% of all admissions to the medical service of a general hospital.[1] A large autopsy series found a prevalence of 0.25% to 0.5% in the general population.[2] ODS occurs most commonly in men between the ages of 30 and 60 years old, as was the case with this patient.

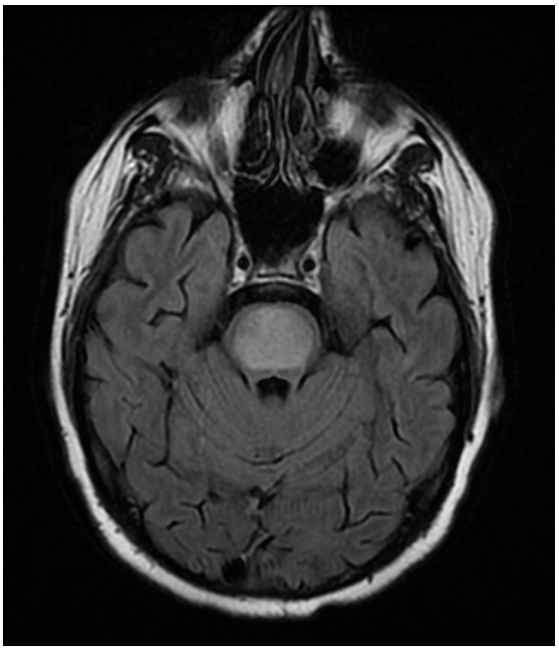
Demyelination typically occurs in areas of the brain that are slowest to uptake osmolytes, which most commonly include the central pons (30%-50%), extrapontine sites (20%-50%), or both the central pons and an extrapontine area (30%-50%).[1-3] The most common extrapontine sites in order of decreasing frequency include the cerebellum, lateral geniculate body, hippocampus, cerebral cortex, thalamus, caudate nucleus, internal capsule, midbrain, and mammillary body.[1,2,4]

The exact amount of osmotic stress necessary to induce ODS is currently unknown. Rates of sodium correction greater than 10 mEq/L per 24 hours or 18 mEq/L per 48 hours are cited as thresholds—though slower rates of sodium correction in patients at increased risk of ODS also have been associated with its development.[2,5] Risk factors for ODS include patients with chronic alcoholism, history of liver transplant, rapid correction of hyponatremia, and malnutrition.[2,6]

Prior to 1994, mortality for ODS at 3 months was described as high as 90% to 100%.[1,2,7] More recent studies cite that approximately 28% to 40% of patients with ODS recover without any neurologic abnormalities, 25% to 33% remain severely incapacitated, and 6% to 9% die.[1,2,8,9] Neither clinical nor radiological features are predictive of which category a given patient will fall into.[1,4] Poor prognostic factors for ODS include low GCS when hospitalized, severe hyponatremia ≤115, hypokalemia, or any pontine involvement.[8,10] In this case, the patient had 3 poor prognostic indicators.

Approximately 2 to 6 days following a rapid rise in serum sodium levels, patients with ODS present with Parkinsonism (44%-50%), quadriparesis, "Locked-in" syndrome, coma, bulbar palsy, or less frequently with dysphagia, dysarthria, facial paresis, ataxia, nystagmus, tremor, lethargy, confusion, behavioral disturbances, and/or disorientation.[1,2,5] Alternatively, symptoms and radiologic findings may be delayed as long as 16 days.[1] A negative MRI cannot rule out ODS and should be repeated in 15 days with diffusion weight imaging, T2-weighted images, and fluid-attenuated inversion recovery (FLAIR) images without contrast if clinical suspicion for ODS remains high.[1]

Figure. T2 FLAIR Image Depicting an Abnormal, Hyperintense Central Pontine Signal With No Associated Restricted Diffusion.



Abbreviation: FLAIR, fluid-attenuated inversion recovery.

Treatment cited in the literature is varied and frequently multifaceted. Reintroduction of hyponatremia following a rapid correction of hyponatremia in murine models reduces neurological manifestations, prevents further myelinolysis, and improves survival by up to 94%.[11,12,13]

Benefit in humans has been demonstrated in 2 case reports but not in a third.[8,10,14] However, those reports did not discuss how to best induce hyponatremia. The reintroduction of hyponatremia in this patient was based upon clinical experience only and not on any predefined protocol. We pursued this first as it had the most literature to support its utility and the lowest risk for adverse effects and excessive health care costs. Methylprednisolone was added due its ability to potentially reduce inflammation, which in the setting of no current infections posed a low overall risk, especially when given for only a few days.

Given minimal clinical improvement and data from multiple studies showing an improvement in neurological symptoms in patients with CPM with the use of IVIg, we initiated this treat-

ment next. IVIg may work by binding to myelinotoxic substances, thereby stopping any further breakdown of myelin. Another possible effect is the immunoglobulins may act as a glue to help bring the myelin together to assist with the repair process, though this is very much speculative. Given small improvements in neurological status with IVIg, we started plasmapheresis as another method to remove possible myelinotoxic substances.

As demonstrated in this case, as well as numerous other cases in the literature, improvement is usually seen early in treatment but may be delayed for up to 4 years.[15] ODS, previously thought to have a dismal prognosis, may yield a meaningful recovery if quickly recognized and appropriately treated.

Funding/Support: None declared.

Financial Disclosures: None declared.

REFERENCES

1. de Souza A. Movement disorders and the osmotic demyelination syndrome. *Parkinsonism Relat D*. 2013;19:709-716.

2. King JD, Rosner MH. Osmotic demyelination syndrome. A*m J Med Sci*. June 2010;339(6):561-567.

3. Verbalis J, Goldsmith S, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med*. 2013; 126(10 suppl 1) S1-42.

4. Martin RJ. Central pontine and extrapontine myelinolysis: the osmotic demyelination syndromes. J *Neurol Neurosurg Psychiatry*. 2004;75(suppl 3):iii22-28.

5. Chang KY, Lee IH, Kim GJ, Cho K, Park HS, Kim HW. Plasma exchange successfully treats central pontine myelinolysis after acute hypernatremia from intravenous sodium bicarbonate therapy. *BMC Nephrol*. 2014;15(56).

6. Murthy SB, Izadyar S, Dhamne M, Kass JS, Goldsmith CE. Osmotic demyelination syndrome: variable clinical and radiologic response to intravenous immunoglobin therapy. *Neurol Sci*. Apr 2013;34(4):581-584.

7. Ludwig KP, Thiesset HF, Gayowski TJ, Schwartz JJ. Plasmapheresis and Intravenous Immune Globulin Improve Neurologic Outcome of Central Pontine Myelinolysis Occuring Post Orthotopic Liver Transplant. *Ann Pharmacother*. Feb 2011; 45(2):e10

8. Kallakatta RN, Radhakrishnan A, Fayaz RK, Unnikrishnan JP, Kesavadas C, Sarma SP. Clinical and functional outcome and factors predicting prognosis in osmotic demyelination syndrome (central pontine and/or extrapontine myelinolysis) in 25 patients. *J Neurol Neurosurg Psychiatry*. 2011;82(3):326-331.

9. Menger H, Jörg J. Outcome of central pontine and extrapontine myelinolysis (n=44). *J Neurol*. 1999;246(8):700-705.

10. Hagiwara K, Okada Y, Shida N, Yamashita Y. Extensive central and extrapontine myelinolysis in a case of chronic alcoholism without hyponatremia: a case report with analysis of serial MR findings. *Intern Med*. 2008;47(5):431-435.

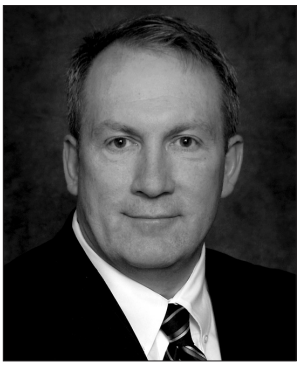
11. Bibl D, Lampl C, Gabriel C, Jüngling G, Brock H, Köstler G. Treatment of central pontine myelinolysis with therapeutic plasmapheresis. *Lancet*. 1999;353(9159):1155.

12. Gankam Kengne F, Soupart A, Pochet R, Brion JP, Decaux G. Re-induction of hyponatremia after rapid overcorrection of hyponatremia reduces mortality in rats. *Kidney Int*. 2009;76(6):614–621.

13. Soupart A, Penninckx R, Stenuit A, Perier O, Decaux G. Reinduction of hyponatremia improves survival in rats with myelinolysis-related neurologic symptoms. *J Neuropathol Exp Neurol*. 1996;55(5):594–601.

14. Takei Y, Akahane C, Ikeda S. Osmotic demyelination syndrome: reversible MRI findings in bilateral cortical lesions. *Intern Med*. Sep 2003;42(9):867-870.

15. Sai Kiran NA, Mohan D, Sadashiva Rao A, Assis ZA, Thakar S, Hegde AS. Reversible extrapyramidal symptoms of extrapontine myelinolysis in a child following surgery for craniopharyngioma. *Clin Neurol Neurosurg*. Jan 2014;116:96-98.



Jon A. Lehrmann, MD

Joseph E. Kerschner, MD

Working to Increase Access to Mental Health Care in Wisconsin

Jon A. Lehrmann, MD; Joseph E. Kerschner, MD

Access to mental health care is a crisis in the United States and much of the rest of the world. There are a number of underlying factors which have led to this predicament, including an incomplete (but positive) emerging understanding that mental illness impacts a substantial percentage of individuals, and that with appropriate intervention, positive outcomes are achievable. According to the Centers for Disease Control and Prevention, about 25% of Americans experience some form of mental illness and close to 50% will develop at least 1 mental illness within her or his lifetime.[1] In addition, there has been an incomplete, although positive, reduction in the stigma surrounding an admission of mental illness and the openness of individuals seeking treatment—both of which have contributed to an increased demand for mental health care and professionals. Further, public/governmental policy and health care system strategies have undervalued investment in both personnel and infrastructure for those individuals seeking care. All of these forces have resulted in an aging mental health professional workforce and lack of access, which is arguably the single most important impediment to overall health and well-being in society today.[2] These difficulties are further exacerbated in less populated areas of the United States where access to mental health professionals is even more challenged.[3]

Unfortunately, only a few initiatives have been offered to remedy these difficulties.

During the past 5 years, however, the Medical College of Wisconsin (MCW) has embarked upon a strategic plan to address this issue in our state that we hope can be replicated in other locations as well. The first step in this process was to create a unique regional medical education program that allows a full class of students to complete their entire medical training in proximity to areas in Wisconsin that possess an overall lack of a physician workforce. MCW-Green Bay matriculated its first class of medical students in July 2015, and MCW-Central Wisconsin welcomed its first class of students in July 2016.

MCW recognized, however, that merely providing positions for medical students was only a part of the solution. The creation of additional psychiatry residency positions was necessary for the regional medical school students to support a continuous link from graduation to graduate medical ed-ucation (GME) to matriculation into the profession—directly in the communities where they had received their medical education and training. According to the Association of American Medical Colleges, 68% of doctors who complete all of their training in 1 state end up practicing there.[4] This would suggest a likelihood that psychiatry residents training in less populated areas of Wisconsin would remain in Wisconsin to provide mental health care to the people of those regions. To that end, MCW created regional medical school campuses with an expressed intent to establish regional residency programs by the time the first class of students graduated in May 2018.

In late April, MCW reached an important milestone in achieving this vision of increased mental health care access in Wisconsin, when the Accreditation Council for Graduate Medical Education (ACGME) announced it had given an initial 5-year accreditation to new MCW-sponsored, 4-year psychiatry residency programs, which will train 3 residents per year in central Wisconsin and 4 residents per year in northeastern Wisconsin.

Although MCW's School of Medicine specifically invested resources to initiate the cre-

• • •

Authors are with the Medical College of Wisconsin, Milwaukee, Wis. Dr Lehrmann is the Charles E. Kubly Professor in Psychiatry and Behavioral Medicine and chair of the Department of Psychiatry and Behavioral Medicine; Dr Kerschner is dean, School of Medicine and executive vice president.

ation of these regional campuses and the new residencies, it is important to note that none of these achievements would have been possible without partnerships. Among the most significant is the Veterans Administration (VA), which clinically and financially will support some of the infrastructure and a number of the residency positions in northeastern Wisconsin. The Wisconsin Department of Health Services has been an essential partner as well, via its award of 2 grants of more than $370,000 each to support the development of these new psychiatry residency programs. And more than $3.3 million was awarded to our health care system partners by the state legislature to help establish these programs. Our partners in northeastern Wisconsin include Milo C. Huempfner Green Bay VA Community-Based Outpatient Clinic, Winnebago Mental Health Institute, Wisconsin Resource Center, Bellin Psychiatric Center and Brown County Community Treatment Center; and in Central Wisconsin, Ministry St. Mary's Hospital (Rhinelander), Ministry St. Michael's Hospital (Stevens Point), Wausau and Wisconsin Rapids VA Community-Based Outpatient Clinics, North Central Health Care, Forrest County Potawatomi Health Care, Wood County Human Services, Portage County Health and Human Services, Bridge Health Clinic (Wausau), and Froedtert Hospital (Milwaukee).

The benefits of these partnerships are innumerable. Medical students enrolled in MCW's regional campuses will rotate their training through some of the same clinical sites as those where the residents will train, allowing the students the opportunity to work with residents as required by the Liaison Committee on Medical Education.

Although MCW is endeavoring to innovate in many areas of medical education, establishing these new mental health residencies attached to our regional campuses is likely to be the most significant in improving the health of the citizens of Wisconsin. If even one of the residents from these programs decides to stay in Wisconsin each year and practice in the region where they train, this will result in improved access to mental health care within a decade–which is enormously important. At the heart of this effort is the realization that these two new residency programs will increase the training of psychiatrists in Wisconsin by more than 40%, which assuredly will improve access to mental health care for many of Wisconsin's citizens.

Solutions to difficult problems often face significant inertia, and as a result, innovative, outside-the-box thinking never sees the light of day. Innovation and ingenuity is required to solve Wisconsin's most difficult health care challenges, and we believe that through research and education, lasting solutions can be attained. We are extremely excited to see the impact these new programs will have on the communities we are privileged to serve. A tremendous debt of gratitude is owed to our partner organizations and legislative leaders for their vision, commitment and tenacity in ensuring that these new residencies became a reality.

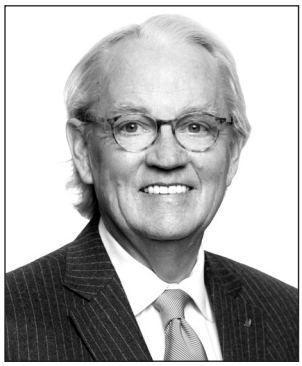
REFERENCES

1. CDC Report: Mental Illness Surveillance Among Adults in the United States. Centers for Disease Control and Prevention. http://www.cdc.gov/mentalhealthsurveillance/fact_sheet.html. Last reviewed Dec 2, 2011. Accessed Dec 15, 2016.

2. Hyde PS. Report to Congress on the Nation's Substance Abuse and Mental Health Workforce Issues. US Department of Health and Human Services. Substance Abuse and Mental Health Services Administration; Jan 24, 2013. https://store.samhsa.gov/shin/content/PEP13-RTC-BHWORK/PEP13-RTC-BHWORK.pdf. Accessed Dec 15, 2016.

3. Evans TW, Berkman N, Brown C, Gaynes B, Weber RP; Investigators. RTI International–University of North Carolina Evidence-based Practice Center, for Agency for Healthcare Research and Quality, US Department of Health and Human Services; May 2016.*Disparities Within Serious Mental Illness*. https://www.effectivehealthcare.ahrq.gov/ehc/products/619/2236/mental-illness-disparities-report-160524.pdf. Accessed Dec 15, 2016.

4. Beitsch R. To Address Doctor Shortages, Some States Focus on Residencies. The Pew Charitable Trusts website. http://www.pewtrusts.org/en/research-and-analysis/blogs/stateline/2015/08/11/to-address-doctor-shortages-some-states-focus-on-residencies. August 11, 2015. Accessed Dec 15, 2016.



What's Keeping You Up at Night?

W. Stancil Starnes, JD

What concerns you most about the practice of medicine right now? I would imagine that declining reimbursement, your electronic medical records system, maintenance of certification, and a host of other items are at the top of your list. But, after years of stability, I believe medical professional liability probably isn't in the top 5.

In many ways, that's understandable as it reflects a medical professional liability climate that is vastly different than a decade ago—when the cost of malpractice insurance was skyrocketing, and the availability of coverage was, at best, uncertain. While the frequency of lawsuits remains largely unchanged over the past 4 to 5 years, loss severity continues to creep up. Thus, I urge you not to let complacency lull you into a false sense of security.

As I said years ago, the most expensive piece of paper you will ever buy may be an insurance policy from a company that will not be there when you need them most. Our goal at ProAssurance, in partnership with the Wisconsin Medical Society (Society), is to ensure that you always will have access to a medical professional liability insurer with unchallenged financial strength and a determination to use that strength along with unparalleled expertise to defend you in the event of a non-meritorious claim.

> ...the most expensive piece of paper you will ever buy may be an insurance policy from a company that will not be there when you need them most.

Our A+ (Superior) rating from A.M. Best was recently affirmed and reinforces ProAssurance's commitment to build the strongest company possible. We want to ensure our policyholders never have any doubts about the company standing behind them.

While that long-term, proven pledge of protection is of paramount importance, you should expect your medical professional liability insurer to deliver value beyond our policy's promised coverage. The ProAssurance partnership with the Society delivers.

The Member Benefit Program (MBP) is a prime example of how ProAssurance and the Society add value. Society members may receive up to a 15% discount on their ProAssurance medical professional liability coverage, and further savings and value are possible for larger groups through the WMS Holdings Risk Purchasing Group, LLC (WMSH RPG). Wisconsin showed the nation how consolidating medicine can maximize delivery of high quality health care through large multispecialty groups; the WMSH RPG allows ProAssurance and the WMSH RPG to respond to the unique needs of Wisconsin's equally unique practice environment.

The work of Bud Chumbley, MD, chief medical advisor for Wisconsin Medical Society Holdings, is assisting the Society. The WMSH RPG supports important patient safety initiatives; it ensures data gleaned from claims and from Risk Resource surveys is integrated into clinical risk management strategies developed in Wisconsin by leading medical/legal and patient safety experts.

Given the everyday threat of cyber liability, the MBP provides added peace of mind through $150,000 of cyber liability coverage

• • •

Stan Starnes is chairman and chief executive officer of ProAssurance Corporation, the parent company of ProAssurance Casualty Company (formerly PIC Wisconsin), the endorsed medical professional liability carrier of the Wisconsin Medical Society.

at no added cost (with higher limits available). As the danger from viruses, theft of electronic records, and data breaches accelerates, our CyberAssurance® coverage will provide MBP insureds with access to experts to guide your response. At the same time, the policy will pay, up to specified limits, regulatory fines and penalties, defense costs for governmental investigations (including HIPAA), and the cost of notifying affected patients—along with appropriate credit monitoring and the recovery or replacement of lost, erased, stolen, or corrupted data.

Our commitment to support and learn from our insureds is another defining feature of ProAssurance's commitment to you and your colleagues. More than 40 Wisconsin physicians, including the Society's Chief Medical Officer Donn Dexter, MD, serve on either a Regional Advisory Board or a statewide Claims & Underwriting Committee. The panels meet 6 a year to review claims and ensure we take into account the nuances of Wisconsin's unique health care system as we underwrite risk in the state. Simply put—our coverage and our claims handling are driven by the physicians we serve.

To help avert a medical incident that could evolve into a medical malpractice lawsuit, we have unveiled new risk management resources from our Risk Resource division. These include online webinars and our series of exclusive "What's the Risk?" videos.

In the past year, we have rolled out an important enhancement for our insured physicians. Our peer-to-peer program, Physicians in Collaboration-Wisconsin (PIC-Wisconsin), supports physicians facing the traumatic effects of a malpractice lawsuit; it connects them, and their families, with ProAssurance-insured physicians who have been through the experience.

No matter how much care is taken, a lawsuit alleging medical malpractice is always a possibility. That's why our proven commitment to the superior defense of nonmeritorious lawsuits is so important.

Every company trying to sell a medical professional liability policy will claim to defend their insureds and provide the best lawyers. We challenge them to prove it. Ask about their trial record—how many cases they defend instead of settle and their success rate in the courtroom. My guess is they either won't tell you, or they won't measure up to ProAssurance. During the 12 months ending June 30, 2016, our tradition of excellence and advocacy continued as we were successful in defending 87.5% of lawsuits tried against Wisconsin insureds.

The bottom line is that I am glad our insureds do not have medical professional liability at the top of their worry list. It means we are doing our job. By delivering on our pledge of Treated Fairly®, ProAssurance allows insureds to focus on their patients and their practices, with one less thing to worry about each day.

Editor's note: The Wisconsin Medical Society helped form PIC Wisconsin in 1985 to ensure the availability of medical professional liability-insurance for Wisconsin physicians. Today the Society continues to endorse ProAssurance (formerly PIC Wisconsin) to provide professional liability insurance coverage for physicians.

Index to Articles: Vol. 115 (2016)

Authors

Articles

Index to Advertisers

Enrolling Now for Spring 2017!
Seating is Limited!

Innovative Leadership

Leading Healthy Work Systems

Why did you choose to become a physician?

How is your medical practice impacted by your colleagues and the system in which you work?

What can you do to influence and lead in a more productive, healthier work environment?

The Wisconsin Medical Society invites you to explore these questions with your physician colleagues in a dynamic new program led by systems and human factors engineer Katherine Sanders, PhD. "Leading Healthy Work Systems" is designed to support you in transforming your work life to better serve patients, lead interprofessional teams and enjoy a more balanced and rewarding life as a healer.

Katherine Sanders has a BS, MS and PhD in Industrial & Systems Engineering from UW-Madison. She specializes in human factors and sociotechnical systems engineering, essentially the health and productivity of people at work. Her academic work as an occupational stress researcher gave rise to a commitment to design programs to support professionals in high burnout occupations. She's one of a small number of PhD systems engineers focused on occupational health, and has a specific interest in the well-being of healers.

When

March 10, April 7 and May 5
9 a.m. to 3 p.m.

Where

Wisconsin Medical Society
Headquarters, Madison, Wis.

Who Should Attend

Physicians in current or emerging leadership roles who are committed to a systems-thinking approach in health care.

This activity has been approved for 15.0 *AMA PRA Category 1 Credits™*.

The Wisconsin Medical Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The Wisconsin Medical Society designates this live activity for a maximum of 15.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Questions?

Call 866.442.3800 ext. 3749,
e-mail todd.wuerger@wismed.org.
or scan this code to visit our website.

Wisconsin Medical Society

THE PHYSICIANS FOUNDATION
Empowering Physicians Improving Healthcare

Wisconsin Medical Society Foundation

Developed by the Wisconsin Medical Society; Funding supported by The Physicians Foundation and the Wisconsin Medical Society Foundation.

Wisconsin Medical Society Insurance & Financial Services, Inc., cares for physicians just like physicians care for their patients. We recognize your unique needs, and we look out for your best interests.

Our agents offer comprehensive protection for physicians and their families. We take great pride in serving **physicians' insurance needs**—including life, disability, health, and long term care insurance.

To learn more, contact insurance@wismed.org, call 866.442.3810 (toll free) or visit our website at wisconsinmedicalsociety.org/insurance.

Wisconsin Medical Society
Insurance & Financial Services, Inc.

Keeping the **game fair...**

...so you're not **fair game.**

Your Wisconsin practice
is getting hit from all angles.

You need to stay focused and on point—
confident in your coverage.

Get help protecting your practice,
with resources that make important
decisions easier.

Proudly Endorsed by

Wisconsin Medical Society
Insurance & Financial Services, Inc.

ProAssurance®
Treated Fairly

SINCE 2007 WARD'S 50 SAFETY • CONSISTENCY • PERFORMANCE

Healthcare Liability Insurance & Risk Resource Services

ProAssurance Group is rated **A+ (Superior)** by A.M. Best.

Want to reduce risk? ›› ProAssurance.com/Seminars

800.282.6242 • ProAssurance.com