ADDITIONAL CONTENT

ORIGINAL RESEARCH & CONTRIBUTIONS
- Development of an Intervention to Reduce Pain and Prevent Syncope Related to Adolescent Vaccination
- Utility of Human Epidermal Growth Factor Receptor 2 (HER2) Retesting of Histologic Grade 3 Invasive Breast Carcinomas
- Adopting YouTube to Promote Health: Analysis of State Health Departments
- Effects of a Group Protocol on Physical Activity and Associated Changes in Mood and Health Locus of Control in Adults with Parkinson Disease and Reduced Mobility
- Evaluation of a Novel Financial Navigator Pilot to Address Patient Concerns about Medical Care Costs

CASE REPORTS
- Prolonged Survival in a Patient with Idiopathic Pulmonary Fibrosis Receiving Acupuncture and DHEA-Promoting Herbs with Conventional Management: A Case Report
- Long-Term Tumor-Free Survival in a Patient with Stage IV Epithelial Ovarian Cancer Undergoing High-Dose Chemotherapy and Vectibix and Pembrolizumab: A Case Report
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NARRATIVE MEDICINE
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Lin Jin, MD; Trupti Y Kapadia, MD; Ann Von Gehr, MD; Efren Rosas, MD; James B Bird, MD; Deepa Ramaswamy, MD; Divyesh Patel, MD

Among 510 patients enrolled during 1 year, 442 (87%) received anemia screening laboratory tests. Half of those with laboratory results were eligible for further optimization: 207 had anemia; 21 had iron deficiency without anemia. Of 228 patients eligible for optimization, 189 (83%) had anemia addressed preoperatively; of 129 patients with iron deficiency anemia, 102 (79%) received intravenous iron preoperatively.

48 Trend of Surgical Treatment of Localized Renal Cell Carcinoma.
Ramzi B Jabaji, MD; Heidi Fischer, PhD; Tyler Kern, MD; Gary W Chien, MD

Rapid adoption of robotics has introduced a paradigm change in prostate cancer treatment, with more than 80% of prostatectomies performed robotically in 2015. From 1/1999 to 9/2015, all Kaiser Permanente Southern California members who underwent surgical treatment of suspected renal cell carcinoma (RCC) were included retrospectively. The study included 5237 patients. During our study, partial nephrectomy became the most common surgery for treatment of localized RCC. Since 2014, robot-assisted laparoscopic partial nephrectomy has become the most common renal oncologic surgical modality in KFSC.
REVIEW ARTICLES

62 Role of Magnetic Resonance Imaging in Diagnosis of Motor Neuron Disease: Literature Review and Two Case Illustrations. Khalid Sawalha, MD; Eduardo Gonzalez-Toledo, MD; Omar Hussein, MD

A literature review and 2 cases with a challenging diagnosis of motor neuron diseases are described, with a thorough discussion of how the diagnosis was suggested on the basis of magnetic resonance imaging evidence in each case. Such findings might enable clinicians to reach an early diagnosis that can improve the patient’s quality of life and prolong survival.

70 Osteonecrosis of the Hip: A Primer. Michelle J Lespasio, DNP, JD, ANP; Nipun Sodhi; Michael A Mont, MD

In this report, the authors deliver a concise and up-to-date review of osteonecrosis, a pathologic, painful, and often disabling condition that is believed to result from the temporary or permanent disruption of blood supply to an affected area of bone. The epidemiology, pathogenesis, etiology, clinical manifestations, diagnosis and classification, and treatment options for hip osteonecrosis are discussed.

CASE REPORTS

77 Prolonged Survival in a Patient with Idiopathic Pulmonary Fibrosis Receiving Acupuncture and DHEA-Promoting Herbs with Conventional Management: A Case Report. Paul Kalnins, MD, NSOM; Mikael Brucker, ND, MAc; Donald Spears, ND, MSOM

A 65-year-old man, diagnosed with idiopathic pulmonary fibrosis in 2007, was being monitored by a conventional pulmonologist while being treated with weekly acupuncture targeting a Chinese medicine diagnosis of spleen dampness and lung qi weakness and with botanical medicine targeting the stimulation of adrenal dehydroepiandrosterone secretion. He survived for 10 years after diagnosis.

83 Long-Term Tumor-Free Survival in a Patient with Stage IV Epithelial Ovarian Cancer Undergoing High-Dose Chemotherapy and Viscum album Extract Treatment: A Case Report. Paul G Werthmann, MD; Robert Kempenich, MD; Gunver S Kienle, MD

Many patients with cancer use Viscum album extracts (VAE). Also called European mistletoe, Viscum album can lead to improved quality of life and reduced chemotherapy side effects and may have synergistic cytotoxic and proliferation-inhibiting effects when used together with chemotherapy. The patient remained tumor-free in follow-up examinations and has enjoyed good health for 20 years after initial diagnosis. Treatment with VAE in this case might have contributed to the reduction of side effects from high-dose chemotherapy and may have acted synergistically with high-dose chemotherapy in tumor control.

IMAGE DIAGNOSIS

86 Image Diagnosis: Thoracic Epidural Hematoma from a Fall Requiring Emergent Decompressive Laminectomy and Hematoma Evacuation. Omar Viswanath, MD; Cyrus Yazdi, MD

Even though the lumbar spinal nerves innervate the lower extremities, and the musculoskeletal and neurologic physical examination of the lower extremities may be largely normal, as in our case, practitioners must be cognizant that there could be cord compression in a more superior location, including the thoracic spine. In addition, patients may have thoracic midline and paraspinal tenderness to palpation on physical examination.

87 ECG Diagnosis: Ibutilide-induced Torsade de Pointes. Daphne D Le; Joel T Levis, MD, PhD, FACEP, FAAEM; Nelya Lugovskaya; David R Vinson, MD

Ibutilide is recommended by professional society guidelines for the cardioversion of atrial fibrillation and flutter. Its rapid effect and minimal impact on hemodynamics make it well suited for use in the Emergency Department. Ibutilide, however, prolongs the corrected QT interval and increases risk for ventricular tachycardia.

HEALTH CARE COMMUNICATION

91 Effect and Durability of an In-depth Training Course on Physician Communication Skills. James T Hardee, MD; Thomas F Rehring, MD; Joseph E Cassara, MD; Karl Weiss, MBA; Nicholas Perrine, PhD

The authors analyzed the effect of a 3-day dedicated course on clinical communication skills among 65 clinicians assessed by a randomized patient survey. Patients were significantly more satisfied with their physician on 6 specific communication skills after the physician received the Communication Skills Intensive training. The effect persisted at 12 months’ follow-up. In addition to the improved patient satisfaction scores, attendees stated that they learned many practical communication skills and valued the course.

COMMENTARY

96 Is There a Lack of Support for Whole-Food, Plant-Based Diets in the Medical Community? Maximilian Andreas Storz, MD

Kaiser Permanente significantly promotes plant-based diets and continuously incorporates plant-based nutrition on the front lines with their dietary recommendations. Despite a continuously growing body of evidence and the meticulous work of renowned experts in this field worldwide, the latest findings in this area have not found their way into US national dietetic guidelines. Why is this the case? What role do physicians play in this context? Is there potentially a lack of support for whole-food, plant-based diets and comprehensive lifestyle change programs in the medical community?

99 Westernized Diet is the Most Ubiquitous Environmental Factor in Inflammatory Bowel Disease. Mitsuho Chiba, MD, PhD; Kunio Nakane, MD, PhD; Masafumi Komatsu, MD, PhD

Representative environmental factors such as smoking, breastfeeding, nonsteroidal anti-inflammatory drugs, antibiotic use in childhood, oral contraceptives, and appendectomy do not correlate with disease onset in most patients with inflammatory bowel disease (IBD). Diets rich in animal protein (risk factor) and deficient in dietary fiber (preventive factor) are characteristic of westernized diets in affluent societies. Recent reports on IBD therapy that replaced westernized diets with plant-based diets achieved far better outcomes than those previously reported in the literature. We believe that westernized diet-associated gut dysbiosis is the most ubiquitous environmental factor in IBD.

NARRATIVE MEDICINE

106 Two Poems. Hospital Chaplain Housekeeping Andrew McLean, MD, MPH

107 My Father’s Dying. Philippa Matras, PhD

GRAPHIC MEDICINE

109 The Great Wall. Stephen Bachhuber, MD
Challenges and Successes with Food Resource Referrals for Food-Insecure Patients with Diabetes

Sanjana Marpadga, MSc1,2; Alicia Fernandez, MD1,2; Jamie Leung3; Audrey Tang, NP3; Hilary Seligman, MD, MAS1,2; Elizabeth J Murphy, MD, DPhil3

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ABSTRACT

Introduction: Clinics increasingly screen patients for food insecurity, but little is known about the efficacy of referring food-insecure patients to community-based food resources.

Objective: To evaluate the implementation of a tailored community food resource referral program in a safety-net diabetes clinic.

Methods: We conducted semistructured phone interviews with food-insecure patients participating in a screening and referral program in a diabetes clinic affiliated with a safety-net hospital. In this qualitative study, we describe barriers to and facilitators of successful food resource referrals from the patient’s perspective.

Results: The prevalence of food insecurity was high (60%). Provision of written and verbal information alone about community food resources resulted in low linkage rates (0%-4%), even with individually tailored referrals. Misperceptions about eligibility, fears around government program registration, inaccessibility, lack of information retention, competing priorities, an inability to cook, stigma, and a perceived sense of stability with existing food support were major barriers to use. Personnel-guided, in-clinic enrollment to a food resource facilitated a higher connection rate (31%).

Discussion: Results of this study suggest that screening for food insecurity followed by a list of food resources for those screening positive may not adequately address patient barriers to using community-based food resources. For food insecurity screening programs in the clinical setting to be effective, systems must not only distribute food resource information but also assist patients in enrollment processes.

INTRODUCTION

Food insecurity is defined as the inability to afford nutritionally adequate and safe foods.1 In 2017, a total of 11.8% of US households were food insecure, with a higher prevalence in households with low socioeconomic status.2 Households at high risk for food insecurity experience cycles of food scarcity, in parallel with “pay cycles” or income shocks.3 This irregularity in food consumption intensifies anxiety over meeting daily dietary needs and results in compensatory behaviors, such as consumption of low-cost, energy-dense foods; skipping of meals when food is unavailable; and binge eating when food is available. Therefore, food-insecure households experience a reduction in the quantity and nutritional quality of food intake. Partly as a result, the risk of diabetes in the US is about 50% higher in food-insecure vs food-secure households.4 For people living with diabetes, food insecurity can significantly increase the risk of hyperglycemic and hypoglycemic episodes,5 lower self-efficacy,6 and reduce financial capacity to make important food and health choices.7

Recognizing the challenges that food insecurity poses to diabetes control, the American Diabetes Association in its 2016 Standards of Medical Care in Diabetes recommended for the first time that clinicians screen for and respond to food insecurity by linking patients with community food resources.8 Given the critical role of food in improving health outcomes as well as preventing and reducing chronic diseases,9 clinics across the country have begun addressing issues related to food access. Recent feasibility studies, primarily in pediatric clinics, have shown that food insecurity screening and referral programs can be successfully implemented in clinics serving low-income, vulnerable populations.10,11 A systematic review of food insecurity screening programs demonstrates the range of strategies adopted by clinics to connect patients with food resources and the need to build evidence for the efficacy of these referrals as a clinical response for patients who screen positive for food insecurity.

We conducted a study to evaluate the outcomes of a tailored food resource referral program in a safety-net diabetes clinic, with a qualitative analysis focused on identifying barriers to and facilitators of successful food resource referrals from the patient’s perspective.

METHODS

Food Insecurity Screening and Resource Referrals

This study was conducted at the Zuckerberg San Francisco General Hospital Diabetes Clinic, a referral site for a network of primary care safety-net clinics in San Francisco, CA. As a component of usual care, 3 trained volunteers screened all patients presenting to the diabetes clinic between November 2014 and November 2015 for food insecurity using the validated Hunger Vital Sign food insecurity screening tool.12 The 2-item screen is widely recommended for clinical screening programs, having demonstrated acceptable sensitivity and specificity in high-risk populations.13 Patients were read the following 2 statements and asked to respond with “often true,” “sometimes true,” or “never true” as each statement applied to them within the past 12 months: 1) “We worried whether our food would run out before we got money to buy more,” and 2) “The food we bought just didn’t last, and we didn’t have money to get more.”

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Keywords: access, diabetes, food, nutrition, public health, safety net, screening, systems
In accordance with standard practice, a response of “often true” or “sometimes true” to at least 1 of the 2 statements was considered a positive screen.18 For patients who were food insecure, volunteers assessed eligibility for specific food resources by collecting information on participant age, zip code, housing status, current benefits, household income, current use of food resources (to prevent unnecessary duplicate referrals), and preferences related to food, cooking, and transportation. Patients were then offered individually tailored, written and verbal information about community food resources, including (as appropriate for the patient) the Supplemental Nutrition Assistance Program (SNAP) and programs offering free groceries, on-site prepared meals (congregate meal sites and free dining rooms, often called “soup kitchens”), and home-delivered meals. At this time, all patients potentially eligible for Project Open Hand, a community-based organization providing medically tailored meals specifically for patients with diabetes, were also offered (and subsequently provided) in-clinic assistance with enrollment into the program.

**Interview Procedures**

From June 2015 through August 2015, all English- and Spanish-speaking patients were approached and separately asked for consent in participation in a 20- to 30-minute follow-up phone interview (with optional audio recording) to be conducted 1 to 4 weeks after the referral. Patients were informed that they would be asked questions regarding their resource referrals. Recruitment and enrollment into the study were done immediately after the food insecurity screening and referral process in the clinic. At the time of the interview, participants had not received any other communication regarding the food resource referrals they had received in the clinic. Participants were first asked whether they were able to follow-up with any resources. If their response was “yes,” the question was followed by probes designed to understand the quality of their experience and the benefits of the food program. For example, participants were asked, “Can you walk me through your experience with this particular food resource?,” “What has been most helpful about this resource?,” and “Can you tell me about any problems you faced contacting or using this resource?” A response of “no” was followed with probes directed at understanding barriers to resource use. Sample questions included “Can you tell me why you have not connected with the resource?“ and “Would you consider using any of the food resources we talked about in the future? Why or why not?”

All interviews with Spanish-speaking patients were conducted with a qualified professional interpreter. Study procedures were reviewed and approved by the Committee on Human Research at the University of California, San Francisco. Patients were not compensated for participating in the study.

**Data Analysis**

We used statistical software (Stata Version 12, StataCorp, College Station, TX) to summarize demographic data and current use of food resources. We analyzed qualitative interviews using the Framework Analysis method,20 adapted for the purposes of our study. The Framework Analysis method identifies themes through an iterative coding process and charting of responses into categories that can be used to identify relationships within the data. One author (SM) transcribed and coded a subset of 11 interviews using an open coding process. The codes were reviewed by 2 other authors (EM and AF), and any disagreements were resolved by discussion. From those interviews, we recognized that patient responses could be consistently grouped into specific categories and began the charting process. We added responses from new interviews to the categories and subsequently reviewed and refined the categories to reflect major concepts across all interviews. We then compared responses in each of the major categories to identify themes and subthemes that emerged. In the Results section, we present themes that were associated with barriers and facilitators to the use of food resources.

**RESULTS**

Among 240 patients who were screened from November 2014 to November 2015, a total of 143 (60%) were food insecure. Demographics are shown in Table 1. More than one-third of food-insecure patients (37%) were using at least 1 food resource at the time of the screening, and nearly 10% were homeless. More than 80% had access to some cooking facilities.

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<tr>
<th>Table 1. Characteristics of food-insecure patients at diabetes clinic</th>
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<td>Age, mean (standard deviation)</td>
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<td>Primary language, no. (%)</td>
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<tr>
<td>English</td>
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<tr>
<td>Spanish</td>
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<tr>
<td>Other</td>
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<tr>
<td>Housing status, no. (%)</td>
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<td>Households with cooking facilities</td>
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<td>Households without cooking facilities</td>
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<td>Homeless</td>
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<tr>
<td>Patients using at least 1 food resource at time of screening, no. (%)</td>
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<tr>
<td>Food resources used at time of screening, no. (%)</td>
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<tr>
<td>Food stamps</td>
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<tr>
<td>Free groceries (eg, food pantries)</td>
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<tr>
<td>Free meals (eg, soup kitchens)</td>
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<td>Home-delivered meals</td>
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* Difference is statistically significant (p < 0.05).

**N = 109. This question was added after a few weeks of screening as we learned the importance of cooking facilities, storage, etc. in making the referrals.

More than 1 response was allowed.
Most patients had not accessed food resources a month after receiving in-clinic referrals. Patients identified barriers to connecting with food resources that highlighted the importance of immigration status, resource accessibility, information retention, competing priorities, cooking/storage ability, stigma, and a perceived sense of stability. However, successful linkage with Project Open Hand revealed that program enrollment guided by clinic staff and the high accessibility of program services had a noticeable positive impact on the outcome of referrals. Table 3 presents a quantified analysis of the themes.

### Barriers to Food Resource Use

#### Perceived Ineligibility

Fear of possible immigration or legal repercussions emerged as an important barrier to connecting with a food resource. Follow-up interviews revealed discomfort in in-clinic discussion of specific eligibility requirements, such as documentation of income and immigration status. One patient said:

*I’m worried because the truth is that I don’t have documentation of my income because I don’t work for a family, and they pay me in cash.* [translated from Spanish]

Some patients believed utilization of community-based food resources would jeopardize their SNAP benefits or immigration processes and thus made no attempt to connect with resources.

*My husband was in the process of becoming a resident, and I was worried that if you get some government help, they would deny or something like that.*

#### Inaccessibility

The most frequently cited barrier to connection with food resources was inaccessibility. Participants noted a lack of transportation to intake appointments, conflicting work schedules, and competing priorities.

### Table 3. Themes and quotes from interviews

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<tr>
<th>Theme</th>
<th>Percentage of all patients*</th>
<th>Illustrative quote</th>
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<tr>
<td>Barriers to connecting with food resource after referral</td>
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<tr>
<td>Perceived ineligibility</td>
<td>5</td>
<td>“I’m worried because the truth is that I don’t have documentation of my income because I don’t work for a company. I work for a family, and they pay me in cash.” [translated from Spanish]</td>
</tr>
<tr>
<td>Inaccessibility (ie, location, hours of operation, long wait times in line)</td>
<td>45</td>
<td>“(I)” depends how far and where the place is. Because I take the bus. I don’t drive. That’s the only problem. I shop myself. I take the bus.”</td>
</tr>
<tr>
<td>Lack of information retention</td>
<td>35</td>
<td>“I just didn’t remember.”</td>
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<td>Competing priorities (ie, employment, housing)</td>
<td>39</td>
<td>“You know, it’s not on my agenda. I’ve been so busy looking for work, so I have other things to do. … But I’d like to.”</td>
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<tr>
<td>Inability to cook</td>
<td>10</td>
<td>“In my room, no [I don’t have a place to cook].” [translated from Spanish]</td>
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<tr>
<td>Stigma</td>
<td>10</td>
<td>“Well, I was getting a little self-conscious about … standing in line to get food or anything like that. So I haven’t really done anything.”</td>
</tr>
<tr>
<td>Perceived stability</td>
<td>29</td>
<td>“I tend to spend more of my energy trying to do something productive than trying to seek out options for food sources when I already have a few that should be working pretty well.”</td>
</tr>
<tr>
<td>Facilitators to connecting with food resource after referral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facilitated enrollment</td>
<td>40</td>
<td>“[If] there’s the chance that I get, you know, just really write the application and then someone called me. And then [they] were here with the food. … It’s amazing!”</td>
</tr>
<tr>
<td>Accessibility (ie, location, delivery options, no queuing)</td>
<td>50</td>
<td>“It’s just convenient. Because otherwise I get into the habit of getting what I can get quickly and it’s not what I should be eating at the time. … Just not having to worry about, you know, if I’m having dinner at 6 or at 9 or if I’m even having dinner at all helps me, you know, with my diabetes in terms of what medicines I have to take or not take.”</td>
</tr>
</tbody>
</table>

* For facilitators, numbers are percentage of all patients who connected with a food resource (n = 10).
long wait times, and an inability to travel alone as a result of physical disabilities.

If you’re working and you’re poor, you don’t have time to go get in line. If you’re unemployed, … you have time for that. Usually, I’m working.

**Lack of Information Retention**

More than one-third of participants (35%) explicitly stated that they did not remember receiving a food resource referral. However, an interview prompt was often sufficient to trigger the memory of previously received referrals.

**Competing Priorities**

For several patients, other priorities (employment, housing, etc) took precedence over finding food support. For example, one patient recently released from prison prioritized his need for housing and safety.

The problem I’m having right now is I don’t actually have a residence. … All my medication is in the trunk of my car. … It’s really been a struggle. Not because of what I’ve been eating but because I don’t actually have a place to put things in a drawer.

**Inability to Cook**

Some patients noted that the lack of safe or clean cooking facilities and/or storage facilities limited their ability to take advantage of free grocery programs.

**Stigma**

Patients reported feeling stigmatized by use of food resources historically associated with poverty, particularly those requiring queuing in long lines, such as free meal programs.

In society, when they see you, … they discriminate [against] you when you’re homeless. When they see you make the line, they don’t just think that you’re homeless and don’t have money. They just think that you’re something bad.

**Perceived Stability**

Despite screening positive for food insecurity, a few patients expressed contentment with existing food support from family, friends, and/or community food resources.

**Facilitators to Food Resource Use**

**Active Enrollment in the Clinical Setting**

One of the most frequently cited factors that helped connect patients with food resources was an active enrollment process, which removed the burden of enrollment from the patient. Patients explicitly stated that the opportunity to have clinic volunteers initiate the enrollment process in-clinic (as was the case for Project Open Hand but none of the other food resources) served as a primary reason they connected with a program. Follow-up phone calls from Project Open Hand staff to set up an intake appointment also supported connection. Staff called multiple times if the patient could not readily be reached by phone.

[He]‘s the chance that I got, you know, just really write the application, and then someone called me. And then [they] were here with the food. … It’s amazing!

**Accessibility**

Convenience and ease of use also emerged as major facilitators to food resource use. For example, patients were more likely to use resources that offered a delivery option or were in their neighborhood.

You know that anyway they [food resources] need to [know] my address because sometimes, I’m too sick to walk. Sometimes, I don’t feel so good. … Sometimes, I get so tired, I can’t walk too much.

**DISCUSSION**

In this study of patients with diabetes identified as experiencing food insecurity, the provision of individually tailored food resource information, as currently recommended by the American Diabetes Association,10 was largely ineffective in improving food access. Barriers to connecting with food resources included concerns regarding immigration status, lack of information retention, inaccessibility, lack of cooking facilities, competing priorities, social stigma, and perceived stability with existing food support. This study has important implications because findings suggest that simply screening and providing a list of food resources may not successfully support food security. However, the results show that patients assisted with enrollment into a food program while in the clinic were able to increase their access to food.

As evidence supporting feasibility of food insecurity screening and referral programs strengthens, the need to assess the success of these interventions becomes imperative. Knowles et al15 recently showed that in a pediatric clinic, clinicians were highly receptive to in-clinic screening for food insecurity. However, passive referrals that were not tailored to patient needs and preferences led to low linkage rates. Smith et al14 reported on successful implementation and feasibility of food insecurity screening and resource referral for adult patients in student-run free clinics. This referral program included data on patients with diabetes, and, although the rate of successful connection with food resources was not quantified, it was noted that connection with offsite resources was low in comparison to the onsite food distribution available at the clinic. This is consistent with the findings of our study.

At the Zuckerberg San Francisco General Hospital Diabetes Clinic, a safety-net diabetes clinic, the prevalence of food insecurity was extremely high (60%) and consistent with rates noted in other safety net clinical settings.14,21 Food-insecure patients who successfully connected with a food resource did so almost exclusively with a single program, Project Open Hand, which involved active enrollment facilitated by staff in the clinic. When asked why they used Project Open Hand, patients discussed the ease of submitting an application. Those enrolled in Project Open Hand chose to use both the home-delivered meals and free grocery pickup programs, suggesting that active enrollment and not home delivery alone were key to the success of this resource. Completing the application in the clinic helped bypass and problem-solve many identified barriers, including information retention, misperceptions about eligibility criteria, and accessibility. The in-clinic process also may have alleviated patient stress around navigating a new system, serving as an important facilitating factor because of the anxiety and decreased cognitive bandwidth often experienced by food-insecure individuals.2,22,23 Additionally, Project Open Hand’s multiple attempts at scheduling appointments increased its accessibility. Finally, as a result of the clinic-assisted referrals, clinic staff were able to follow-up on patient enrollment status.
This study underscores the difficulty of successfully improving food access for food-insecure patients through referrals to community-based federal and local food assistance programs as recommended by current guidelines.\textsuperscript{9,10,12,14} Competing priorities, inaccessibility, a lack of cooking facilities, and social stigma were major barriers to connecting with food resources. Concerns related to immigration status and the impact of applying for and/or receiving food resources were also evident. These barriers involve much broader socioeconomic, cultural, and political factors that were not addressed by our intervention but may be critical factors in confronting food insecurity and highlight the need to be patient-centered in designing successful intervention programs.

This study has several limitations. The interview sample was small and limited to English- and Spanish-speaking patients receiving care with phone access at a specialty safety-net clinic and therefore is not generalizable to all patient populations. Because of language limitations, we oversampled English-speaking patients. However, we believe the themes identified are broad enough to reflect important factors that influence successful uptake of food resource referrals among low-income populations served by the clinic. Furthermore, 88% of the clinic’s food-insecure patients were Spanish- or English-speaking, suggesting that the study’s interview sample highlights themes that are critical for a majority of the clinic’s patient population. Our small sample size also precludes quantitative analysis between the demographics of patients who connected with Project Open Hand and those who did not. However, understanding these differences is critical to implementing effective referral programs and should be explored in future research. Finally, responses to the qualitative interview questions may have been subject to social desirability bias.

**CONCLUSION**

Access to healthy food is critical to achieving optimal diabetes outcomes. Effective in-clinic food resource referral processes are urgently needed given the clear importance of food security in achieving optimal diabetes outcomes\textsuperscript{8,9,21,25} and the increasing emphasis on screening for food insecurity in high-risk clinical settings.\textsuperscript{9,10,12,14} The marked failure of simple written and verbal provision of resources—even when tailored for eligibility and location—and the success of clinic-assisted enrollment processes highlight the need to build community-clinic linkages that support enrollment assistance, information sharing, and communication between clinics serving high-risk populations and community-based food programs. These systems-level changes can be critical to addressing food insecurity in the safety net setting.

**Disclosure Statement**

The author(s) have no conflicts of interest to disclose.

**Author Contributions**

Sanjana Marpadga, MSc, contributed to the study design, collected the data, analyzed the data, and wrote the manuscript. At the time the data were collected, Sanjana Marpadga, MSc, was a student in the Master of Science in Global Health Sciences program at the University of California, San Francisco. Elizabeth J Murphy, MD, DPhil, and Alicia Fernandez, MD, contributed to the project design and data analysis and reviewed and edited the manuscript. Hilary Seligman, MD, MAS, contributed to study design and reviewed and edited the manuscript. Jamie Leung assisted with study design and patient enrollment and reviewed the manuscript. Audrey Tang, NP, collected data, assisted with study design, and reviewed the manuscript.

**Acknowledgments**

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Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

**How to Cite this Article**


**References**

The longer I live the less confidence I have in drugs and the greater is my confidence in the regulation and administration of diet and regimen.

— John Redman Coxe, MD, 1773-1864, American physician, medical educator, and writer
Association of Adverse Childhood Experiences with Depression in Latino Migrants Residing in Tijuana, Mexico

Pedro Kremer, MD, MPH; Monica Ulbrich, PhD; Natalie Ferraiolo, MD; Miguel Pinedo, PhD; Adriana Carolina Vargas-Ojeda, MD, PhD; Jose Luis Burgos, MD, MPH; Victoria D Ojeda, PhD, MPH

Original Research & Contributions

ABSTRACT

Context: Physical, sexual, and emotional abuse in childhood—adverse childhood experiences (ACEs)—are associated with poor mental and physical health.

Objective: To determine the prevalence of ACEs and their relationship to depression among Latino migrants in Mexico, which has not been previously examined.

Methods: A total of 110 Latinos aged 18 years and older residing in Tijuana, Mexico, completed interviewer-administered questionnaires, including the ACE scale (range = 0 to 10 items), at baseline in 2015. We studied the prevalence of ACEs (score on the ACE scale) and the presence of depressive symptoms (Patient Health Questionnaire-9). Multivariate logistic regression models were used to estimate the association between the ACE score and depressive symptoms.

Results: Overall, 82% of participants were men, and 82% reported being deported from the US. At least 1 ACE was reported by 64% of participants, and 33% reported 3 or more ACEs. Those who reported ever being incarcerated were significantly more likely to have 3 or more ACEs compared with no ACEs (56% vs 28%; p = 0.039). Symptoms of mild, moderate, or severe depression were identified in 14% of participants. In multivariate analyses, for each additional ACE item reported, participants were significantly more likely to meet criteria for depressive symptoms (adjusted odds ratio = 1.42; 95% confidence interval = 1.13-1.78; p = 0.002).

Conclusion: Among Latino migrants residing in the US-Mexico border region, ACEs were pervasive and associated with depression symptoms. Programs and policies targeting migrants in this region should consider addressing both ACEs and depression.

INTRODUCTION

Exposure to repeated or multiple emotional trauma is linked to mental and physical health conditions, including anxiety disorders, major depression, and heart disease; traumatic events occurring during childhood can be particularly harmful. Adverse childhood experiences (ACEs) are defined as traumatic experiences that occur before age 18 years. Exposure to traumatic events can be assessed via the 10-item US Centers for Disease Control and Prevention-Kaiser Permanente ACE scale; it was validated in more than 17,000 US adults. The scale probes for experiences of abuse, neglect, and household dysfunction. Such ACEs have been proposed to disrupt neurodevelopment and increase the likelihood of mental health disorders.

Although ACEs have been examined in American populations, including US-based Latinos, the largest study of the association between traumatic childhood events and depression in later stages of life was conducted in a mostly white, middle- and upper-class, and educated population affiliated with a large health maintenance organization. The ACE scale has subsequently been fielded in diverse populations. The current study assesses the prevalence and relationship between ACEs and depression symptoms in a sample of Latino migrants residing in Tijuana, Mexico, a major migrant- and deportee-receiving community. This study provides insight into factors that may affect Latino migrants’ mental health.

In both the US and Mexico, childhood abuse and neglect are concerning social and public health issues. In the US, approximately 3.2 million children reported abuse or neglect in 2014. Childhood abuse, a dimension of the ACE scale, has been associated with subsequent development of mental health problems, including posttraumatic stress disorder, borderline personality disorder, dissociative symptoms, and depression. In Mexico, 62% of boys and girls have experienced abuse at some point in their lives, and the prevalence has increased by 50% between 2013 and 2015.Neglect (27%) and physical abuse (23.7%) are the most prevalent forms of childhood abuse in Mexico. A 2008 study examining ACEs among 178 pregnant women in Mexico City, Mexico, reported that 60% experienced at least 1 ACE; 45% of women reported physical abuse, and 47% reported problematic parental alcohol consumption. The prevalence of ACEs in a Mexican internal migrant or Mexico-US transnational migrant population is unknown, as are implications for resilience after these traumatic events.

Depression is also pervasive, and the Centers for Disease Control and Prevention estimates that it affects 7.6% of persons age 12 years or older in the US. In Mexico the reported prevalence of depression ranges between 12% and 20%, but other studies showed higher rates (20%-59%) in US-Mexico border populations. This study complements prior literature by examining the experiences of a largely male migrant population.

Given the relationships between mental illness and physical health, it is important to further elucidate potential contributors to poor mental health in adulthood. Such data can support the development
or implementation of interventions to prevent or to treat mental illness across the life course. This study aims to 1) assess the prevalence of ACEs among Latino migrants in Tijuana and 2) assess the relationship between ACEs and current depression symptoms in this population.

**METHODS**

**Study Setting, Design, and Participants**

This study examined baseline questionnaire data collected from 110 adults aged 18 years and older participating in a tattoo removal study. The study site was a free clinic situated in the Zona Norte (Tijuana’s red-light district). Clinic patients included very poor, homeless, and uninsured individuals as well as injection drug users. The clinic advertised the tattoo removal study widely via posters inside consultation rooms and in windows facing the community, so that any individual aged 18 years and older was eligible to be screened for participation. The sample for this study is composed of community members and the clinic’s patients, although we are unable to differentiate the number of persons that comprise these 2 groups. The clinic’s patients are primarily migrants (ie, migrants to the US, migrants within Mexico, or international migrants from other countries, such as Central America).

The parent study involved the screening of 147 participants, of which 22 were excluded for the following reasons: Breastfeeding (n = 1), color tattoos (n = 14; these persons were excluded because the laser was not designed to remove non-black tattoos), positive HIV test or HIV test refusal (n = 4), and short-term plans to relocate away from Tijuana (n = 3). These individuals did not undergo baseline interviews. Among the remaining 125 participants, 15 were excluded because of the absence of data corresponding to the ACEs scale. Thus, the final sample was composed of 110 individuals.

Trained bilingual interviewers administered questionnaires to the participants in a private room using Qualtrics cloud-based questionnaire software (Qualtrics, Provo, UT). The study protocol was approved by the human subjects protection programs at the University of California San Diego, the Universidad Autónoma de Baja California, Tijuana; and the free clinic where the study was implemented.

**Measures**

The baseline (Spanish or English) questionnaire (lasting approximately 45 minutes) addressed the following topics: 1) demographics (eg, age, sex, marital status, homeless status, self-rated economic status, employment status, and

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**Table 1. Adverse Childhood Experiences (ACE) scale and item prevalence and depression prevalence in a community sample of adults attending a free health care clinic in Tijuana, Mexico in 2015 (N = 110)**

<table>
<thead>
<tr>
<th>Category</th>
<th>ACE scale question</th>
<th>No. (%)</th>
<th>Depression, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abuse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>Before your 18th birthday, did a parent or other adult in the household often or very often swear at you, insult you, put you down, or humiliate you? Or act in a way that made you afraid that you might be physically hurt?</td>
<td>35 (31.8)</td>
<td>8 (22.8)</td>
</tr>
<tr>
<td>Physical</td>
<td>Before your 18th birthday, did a parent or other adult in the household often or very often push, grab, slap, or throw something at you? Or ever hit you so hard that you had marks or were injured?</td>
<td>32 (29.1)</td>
<td>8 (25.0)</td>
</tr>
<tr>
<td>Sexual</td>
<td>Before your 18th birthday, did an adult or person at least 5 years older than you ever touch or fondle you or have you touch their body in a sexual way? Or attempt to have or actually have oral, anal, or vaginal intercourse with you?</td>
<td>19 (17.3)</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td><strong>Household dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother treated violently</td>
<td>Before your 18th birthday, was your mother or stepmother often or very often pushed, grabbed, slapped, or had something thrown at her? Or sometimes, often, or very often, kick, bitten, hit with a fist, or hit with something hard?</td>
<td>19 (17.3)</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>Household substance abuse</td>
<td>Before your 18th birthday, did you live with anyone who was a problem drinker or alcoholic, or who used street drugs?</td>
<td>37 (33.6)</td>
<td>8 (21.6)</td>
</tr>
<tr>
<td>Household mental illness</td>
<td>Before your 18th birthday, was a household member depressed or mentally ill, or did a household member attempt suicide?</td>
<td>14 (12.7)</td>
<td>5 (35.7)</td>
</tr>
<tr>
<td>Parental separation or divorce</td>
<td>Before your 18th birthday, was a biological parent ever lost to you through divorce, abandonment, or other reason?</td>
<td>25 (22.7)</td>
<td>7 (28.0)</td>
</tr>
<tr>
<td>Incarcerated household member</td>
<td>Before your 18th birthday, did a household member go to prison?</td>
<td>29 (26.4)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td><strong>Neglect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional</td>
<td>Before your 18th birthday, did you often or very often feel that no one in your family loved you or thought you were important or special? Or that your family didn’t look out for each other, feel close to each other, or support each other?</td>
<td>26 (23.6)</td>
<td>7 (26.9)</td>
</tr>
<tr>
<td>Physical</td>
<td>Before your 18th birthday, did you often or very often feel that you didn’t have enough to eat, had to wear dirty clothes, and had no one to protect you? Or that your parents were too drunk or high to take care of you or take you to the doctor if you needed it?</td>
<td>24 (21.8)</td>
<td>6 (25.0)</td>
</tr>
</tbody>
</table>

* Percentage of participants with depression is based on the number shown in the No. (%) column to the left.
possession of a Mexican Federal Voter Identification [ID] card—Mexico’s main government identification; 2) US migration and incarceration history, either in Mexico or the US; 3) drug use (lifetime); 4) lifetime self-reported health diagnoses of chronic conditions by a clinician; and 5) self-rated health status. In the next paragraph, we provide additional details for these variables.

The Mexican Voter ID Card was included in this analysis because it is a required document for accessing federally funded health and social programs in Mexico; possession of this ID was ascertained via a yes/no question. Homeless status was a dummy variable created from the question “Where did you sleep most of the nights during the last 6 months?” and homelessness was registered for every participant who answered affirmatively to at least 1 of the following options: A church, a drug dealer’s house, a shelter, the streets, by the river, an abandoned building, or a park. Self-rated economic status was ascertained by the question “How do you define your current economic situation?” and homelessness was registered for every participant who answered affirmatively.

Table 2. Participant characteristics stratified by number of adverse childhood events (ACEs), in adults aged 18 years and older attending a free health care clinic in Tijuana, Mexico in 2015

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of ACE items, n (%)</th>
<th>Total (N = 110)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 items, 40 (36)</td>
<td>1 or 2 ACEs, 34 (31)</td>
<td>≥ 3 ACEs, 36 (33)</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>35 (88)</td>
<td>29 (85)</td>
<td>26 (72)</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>41 (8)</td>
<td>41 (9)</td>
<td>40 (9)</td>
</tr>
<tr>
<td>Has voter ID card</td>
<td>25 (63)</td>
<td>27 (79)</td>
<td>22 (61)</td>
</tr>
<tr>
<td>Cohabiting partner</td>
<td>12 (30)</td>
<td>17 (50)</td>
<td>11 (30)</td>
</tr>
<tr>
<td>Homeless</td>
<td>28 (70)</td>
<td>21 (58)</td>
<td>23 (63)</td>
</tr>
<tr>
<td>Poor/very poor economic status</td>
<td>27 (68)</td>
<td>19 (56)</td>
<td>20 (56)</td>
</tr>
<tr>
<td><strong>Traumatic events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever deported</td>
<td>26 (79)</td>
<td>25 (83)</td>
<td>24 (86)</td>
</tr>
<tr>
<td>Ever incarcerated</td>
<td>11 (28)</td>
<td>16 (47)</td>
<td>20 (56)</td>
</tr>
<tr>
<td>Substance use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever used illegal drugs</td>
<td>28 (70)</td>
<td>29 (85)</td>
<td>33 (92)</td>
</tr>
<tr>
<td>Used illegal injection drugs in last 6 months</td>
<td>14 (41)</td>
<td>14 (47)</td>
<td>17 (49)</td>
</tr>
<tr>
<td><strong>Physical health and disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/moderate/severe depression symptoms</td>
<td>2 (5)</td>
<td>2 (6)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Self-rated fair/poor general health status</td>
<td>5 (13)</td>
<td>10 (29)</td>
<td>10 (28)</td>
</tr>
<tr>
<td>Ever diagnosed with cancer, diabetes, or HIV</td>
<td>17 (43)</td>
<td>16 (47)</td>
<td>16 (44)</td>
</tr>
</tbody>
</table>

* Statistical significance level: p < 0.05.

ID = identification; SD = standard deviation.

Our primary independent variable was the ACE scale, which ranges from 0 to 10 items and includes 3 subcategories: Abuse (3 items), neglect (2 items), and household dysfunction (5 items; Table 1). The dependent variable was the score on the Patient Health Questionnaire-9 (PHQ-9), which has been validated in national US samples, including Latinos, to detect mild depression (5 to 9 points), moderate depression (10 to 14 points), moderately severe depression (15 to 19 points), and severe depression (20 to 27 points). We dichotomized the data as follows: 0 referred to no or minimal depression (ie, PHQ-9 score: ≤ 4 points), and 1 referred to mild/moderate/severe depression (ie, PHQ-9 ≥ 5 points).

**Statistical Analysis**

We conducted descriptive analyses to characterize the study population using χ² or analysis of variance tests for categorical and continuous variables respectively, to compare differences across groups. We examined the proportion of participants reporting each ACE scale item (Table 1). Next, we examined the unadjusted association between our independent variables and number of ACEs, as defined by the number of items reported (ie, 0 ACEs, 1-2 ACEs, ≥ 3 ACEs; Table 2) as well as all independent variables and PHQ-9 scores (Table 3). We estimated a binary logistic regression model to examine the association between the ACE scale (range = 0 to 10 items) with mild/moderate/severe depression (vs no/ minimal depression; Table 4). We also estimated the association between the 3 ACE subcategories and depression (Table 5). Regression models were adjusted for demographics, health status, and economic indicators.
RESULTS
ACE Prevalence and Participant Characteristics
Table 1 provides each ACE item and the proportion of participants that reported each item before their 18th birthday. Overall, household substance abuse (33.6%) and emotional abuse (31.8%) were the most commonly reported ACEs, whereas household mental illness was the least commonly reported item (12.7%). In the abuse category, emotional abuse was most commonly reported (31.8%); in household dysfunction, substance abuse was most prevalent (33.6%); and in the neglect category, emotional neglect was most commonly reported (23.6%). Table 1 also shows the prevalence of depression (ie, ≥ 5 points on the PHQ-9 scale) for each ACE item; it ranged from 20% and 30%, with the exception of household mental illness (36%). Overall, 14% of participants (15 of 110 participants) met criteria for mild, moderate, or severe depression. Additional analyses found that only 10 individuals (9%) met criteria for moderate or severe depression (data not shown); given the small sample, we focused on mild/moderate/severe depression as a combined group.

Table 2 shows participants' characteristics, including stratified by the number of ACEs reported (ie, 0 ACEs; 1-2 ACEs; ≥ 3 ACEs). Slightly more than one-third of participants (36.4%) reported never experiencing ACEs, although most did experience ACEs: 30.9% of participants reported experiencing 1 or 2 ACEs, and 3 or more ACEs were reported by 32.7% of participants. Regarding their demographic and social characteristics, participants were predominantly male (82%) and, on average, were 41 years old; 96% of participants were Mexico-born (data not shown). One-third of participants lacked the Mexican Voter ID card, 65% reported being homeless at the time of the interview, 30% were married or in a civil union, 82% had been deported from the US, and 43% had ever been incarcerated. Additionally, 85% had ever migrated to the US (data not shown). Overall, 60% rated their economic status as poor/very poor. Nearly half of participants reported injecting drugs in the prior 6 months (46%), and 80% mentioned past use of illegal drugs, excluding marijuana. Also, 44% reported having ever been diagnosed with cancer, diabetes, or HIV, and 17% had ever experienced forced sex. About 1 in 4 participants rated their health as fair/poor (23%).

Regarding the relationship between participants' demographic and social characteristics and ACEs, we observed that individuals reporting 3 or more ACEs were more likely to have been incarcerated (56% vs 47% among those reporting 1-2 ACEs and 28% among those reporting 0 ACEs; p = 0.039). Those reporting 3 or more ACEs also were more likely to have ever experienced forced sex (31% vs 15% for reports of 1-2 ACEs and 5% among those reporting 0 ACEs; p = 0.012).

Factors Independently Associated with Depression
Table 4 presents results from a multivariate logistic regression model examining the relationship between ACEs and mild, moderate, or severe depression symptoms.

### Table 3. Bivariate relationship: Participant characteristics and their association with depression symptoms in 110 adults attending a free health care clinic in Tijuana, Mexico in 2015

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Minimum or no depression symptoms, n = 15 (%)</th>
<th>Mild/moderate/severe depression symptoms, n = 95 (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>10 (67)</td>
<td>79 (83)</td>
<td>0.131</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>41 (8.2)</td>
<td>36 (9.5)</td>
<td>0.041</td>
</tr>
<tr>
<td>Voter ID card</td>
<td>10 (68)</td>
<td>57 (60)</td>
<td>0.518</td>
</tr>
<tr>
<td>Cohabiting partner</td>
<td>5 (35)</td>
<td>7 (47)</td>
<td>0.372</td>
</tr>
<tr>
<td>Homeless</td>
<td>8 (55)</td>
<td>60 (63)</td>
<td>0.372</td>
</tr>
<tr>
<td>Poor/very poor economic status</td>
<td>9 (59)</td>
<td>50 (53)</td>
<td>0.682</td>
</tr>
<tr>
<td>Traumatic events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever deported</td>
<td>13 (84)</td>
<td>67 (70)</td>
<td>0.284</td>
</tr>
<tr>
<td>Ever incarcerated</td>
<td>6 (42)</td>
<td>45 (47)</td>
<td>0.740</td>
</tr>
<tr>
<td>Substances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever used illegal drugs</td>
<td>12 (80)</td>
<td>76 (80)</td>
<td>1.000</td>
</tr>
<tr>
<td>Used illegal injection drugs last 6 months</td>
<td>7 (45)</td>
<td>55 (58)</td>
<td>0.376</td>
</tr>
<tr>
<td>Physical health and disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-rated fair/poor general health status</td>
<td>(4)23</td>
<td>26 (27)</td>
<td>0.766</td>
</tr>
<tr>
<td>Ever diagnosed with cancer, diabetes, or HIV</td>
<td>5 (36)</td>
<td>26 (27)</td>
<td>0.490</td>
</tr>
</tbody>
</table>

* Depression symptoms were evaluated using the Patient Health Questionnaire-9. ID = identification; SD = standard deviation.

### Table 4. Logistic regression model of ACE scale and depression symptoms in a community sample of adults ages 18 years and older attending a free health care clinic in Tijuana, Mexico in 2015 (n = 110)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE scale (per additional item)*</td>
<td>1.42</td>
<td>1.13-1.78</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (continuous variable)</td>
<td>0.93</td>
<td>0.86-1.02</td>
<td>0.121</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.77</td>
<td>0.35-8.81</td>
<td>0.483</td>
</tr>
<tr>
<td>Cohabiting partner</td>
<td>1.99</td>
<td>0.46-8.66</td>
<td>0.355</td>
</tr>
<tr>
<td>Homeless</td>
<td>0.41</td>
<td>0.07-2.28</td>
<td>0.284</td>
</tr>
<tr>
<td>Self-rated fair/poor general health status</td>
<td>0.57</td>
<td>0.08-3.90</td>
<td>0.575</td>
</tr>
<tr>
<td>Poor/very poor economic status</td>
<td>3.84</td>
<td>0.72-20.63</td>
<td>0.116</td>
</tr>
<tr>
<td>Ever used illegal drugs</td>
<td>1.97</td>
<td>0.19-20.03</td>
<td>0.566</td>
</tr>
<tr>
<td>Ever diagnosed with cancer, diabetes, or HIV</td>
<td>0.30</td>
<td>0.06-1.50</td>
<td>0.151</td>
</tr>
</tbody>
</table>

* The ACE scale ranges from 0 to 10 items.
ACE = Adverse Childhood Experiences; CI = confidence interval; HIV = human immunodeficiency virus; OR = odds ratio.
(ie, PHQ-9 ≥ 5 points), while controlling for demographic, health, and economic covariates. Results indicate that ACEs are positively associated with mild, moderate, or severe depression, such that the likelihood of depression was significantly increased by 42% for each additional point on the ACE scale (adjusted odds ratio [AOR] = 1.42; 95% confidence interval: 1.13-1.78; p = 0.002). Other variables were not statistically significant in their association with depression symptoms.

Table 5 presents data on the relationship between the 3 ACE subcategories and depressive symptoms; all were statistically significant. In Model 1, which included adjustments for age and sex, the AORs ranged from 1.75 for persons reporting items in the household dysfunction category to 2.15 for persons reporting items pertaining to neglect. These AORs were further elevated in Model 2, which was further adjusted for cohabitating partner status, homelessness, chronic diseases, self-rated health status, employment, and self-reported economic status. This model provided even higher and more homogeneous AORs, ranging between 2.29 and 2.42 for the 3 ACE subcategories.

**DISCUSSION**

This study examined the association between ACEs and depression symptoms in a sample composed primarily of male Latino migrants residing in Tijuana, a metropolis that is a major migrant sending, receiving, and transit community. To our knowledge, this is the first study examining the association between ACEs and depression in a vulnerable sample in the US-Mexico border region. Our results are comparable to those obtained in a recently published meta-analysis that included 184 studies, in which maltreated children were 2.66 (95% confidence interval: 2.38-2.98) to 3.73 (95% confidence interval: 2.88-4.83) times more likely to experience depression in adulthood.4

Our study participants experienced multiple stressors (eg, deportation, homelessness, incarceration) that could have contributed to current depressive symptoms among those who were already vulnerable because of prior ACEs.

Our participants reported a higher prevalence of ACEs than has been reported in US-based populations.1,9 Childhood stressors appear to increase the likelihood of depression in adulthood, and their effect may be compounded by the experience of additional adversity in adulthood. An investigation conducted in newly recruited US soldiers showed that those who experienced episodic emotional maltreatment during childhood were 50% more likely to develop a major depressive disorder shortly after a stressful event.28 Our study participants experienced multiple stressors (eg, deportation, homelessness, incarceration) that could have contributed to current depressive symptoms among those who were already vulnerable because of prior ACEs.

Study limitations include the following. It is difficult to establish causality between ACEs and depression, especially among adults, given that their responses may be affected by recall or social desirability biases. To address generalizability of our findings, it is worth mentioning that our sample has some characteristics (eg, primarily male, high volume of deportees) that preclude further generalizations to the broader population, even in Tijuana. Future studies should include a greater number of participants, especially migrant women, as well as other communities within Tijuana to reduce the possibility of selection bias. Similar studies should be conducted in diverse geographic areas to understand the scope of ACEs across Mexico and Latin America. Additionally, we were unable to corroborate physical health status; this should also be examined in future studies via the use of biomarkers and medical assessments. Because of the stigma associated with experiencing sexual abuse, some degree of underreporting of ACEs is to be expected among men, more so than among women.29-31 Finally, controlling for variables that could be mediators in the association between ACEs and depression (eg, homelessness, chronic diseases) could result in underestimation of the total effect of the traumatic events. Despite these limitations, the findings are robust and consistent with previously published research.

**CONCLUSION**

Our study findings have potential implications for future research and practice. Our analysis expands the existing body of evidence addressing the association between ACEs and adulthood depression. Furthermore, our findings may contribute to the understanding that males, migrants, and deportees living in border regions not only face the challenges of their current circumstances but also past adversity. Resilience in adulthood can be supported by promoting access to mental health services, especially among individuals who are the most socially and economically disenfranchised. Health systems should support the routine use of ACEs as a mental health screening tool; this should be accompanied by training clinicians to implement the ACE scale during clinical

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**Table 5. Logistic regression model of ACE subscales and depression symptoms in adults aged 18 years and older attending a free health care clinic in Tijuana, Mexico in 2015**

<table>
<thead>
<tr>
<th>ACE category</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abuse</td>
<td>1.88</td>
<td>(1.12-3.17)</td>
<td>2.31</td>
<td>(1.27-4.18)</td>
</tr>
<tr>
<td>Neglect</td>
<td>2.15</td>
<td>(1.12-4.15)</td>
<td>2.42</td>
<td>(1.26-5.68)</td>
</tr>
<tr>
<td>Household dysfunction</td>
<td>1.75</td>
<td>(1.21-2.53)</td>
<td>2.29</td>
<td>(1.40-3.72)</td>
</tr>
</tbody>
</table>

ACE = Adverse Childhood Experiences; CI = confidence interval; OR = odds ratio.

Model 1: Adjusted by age and sex.

Model 2: Adjusted by age, sex, cohabiting partner status, homelessness, chronic diseases, self-rated health status, employment, and self-reported economic status.
encounters. Lastly, social support networks for migrants, including migrant-led services, could be promoted to foster and support the recovery process.1,2,3,4

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

Acknowledgment
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References
Patient Education and Pharmacist Consultation Influence on Nonbenzodiazepine Sedative Medication Deprescribing Success for Older Adults

Jennifer L Kuntz, PhD; Louis Kouch, PharmD; Daniel Christian, PharmD; Weiming Hu, MS; Preston L Peterson, MD

ABSTRACT

Introduction: Use of nonbenzodiazepine sedative hypnotics or “Z-drugs”—including eszopiclone, zolpidem, or zaleplon—is discouraged for older adults; however, these medications are prescribed to treat insomnia in this population. We evaluated the impact of direct-to-patient education, with or without a pharmacist consultation, on Z-drug discontinuation among Kaiser Permanente Northwest members age 64 years and older.

Methods: We randomized 150 patients to usual care (UC), educational information only, or educational information and pharmacist consultation. Patients age 64 years and older who received 2 to 3 Z-drug fills in 2016 were included. Logistic regression was used to calculate odds of discontinuation at 6 months among patients who received either intervention, compared with those who received UC.

Results: Patients who received education only and education plus pharmacist consultation were significantly more likely to discontinue Z-drug use than those who received UC (28/50 of those who received education only and 27/49 of those who received education plus consultation vs 13/50 patients who received UC). After controlling for patient demographics, comorbidity, and antianxiety and antidepressant medication use, patients who received education only had greater odds of Z-drug discontinuation than those in the UC group (adjusted odds ratio = 4.02, 95% confidence interval = 1.66-9.77). Patients who received education and a pharmacist call also had greater odds of discontinuing use of these drugs than those in the UC group (adjusted odds ratio = 4.10, 95% confidence interval = 1.65-10.19).

Conclusion: Patients who received direct-to-patient education with or without a pharmacist consultation were significantly more likely to discontinue Z-drug use than patients receiving UC. Providing evidence-based information about Z-drug use risks and empowers patients to initiate discussions with their prescribing clinician about medication discontinuation.

INTRODUCTION

Adults age 64 years and older routinely are prescribed nonbenzodiazepine sedative-hypnotics (“Z-drugs,” which include eszopiclone, zolpidem, or zaleplon) for insomnia treatment despite a lack of evidence that demonstrates these medications improve sleep over the long term and a wealth of evidence that links long-term use with falls, daytime sedation, cognitive impairment, decreased quality of life, dependence, and hospitalization. However, the literature also acknowledges that discontinuing a medication may be just as difficult, if not more difficult, than starting a medication. One approach to deprescribing that holds great promise is direct-to-patient education, which provides information about medication use risks and empowers patients to initiate discussions with their prescribing clinician about medication discontinuation.

Kaiser Permanente Northwest (KPNW) piloted an intervention that sought to encourage deprescribing of Z-drugs among KPNW patients 64 years of age and older. Patients were randomized to receive usual care (UC) or direct-to-patient education with or without a pharmacist consultation. We examined the impact of these interventions on Z-drug discontinuation.

METHODS

In 2017, KPNW, an integrated health care delivery system serving about 580,000 members in Northwest Oregon and Southwest Washington, conducted a pilot implementation of an intervention that used both direct-to-patient education and pharmacist counseling to encourage deprescribing of Z-drugs among older adults. The intervention was implemented by the KPNW health care system as a quality improvement initiative and delivered as part of UC; consequently, the KPNW institutional review board, which reviewed and approved this research, granted a waiver of informed consent.

Patients were eligible for the deprescribing intervention if they were at least age 64 years and received 2 or 3 prescription dispensings of a Z-drug—including eszopiclone, zolpidem, or zaleplon—during 2016. Members were excluded if they had less than 6 months of Health Plan enrollment or if they received a quantity ≤ 6 doses. Members also were excluded if they received palliative or hospice care or resided in an assisted-living facility during the year before randomization. Members were not eligible if they had active cancer, severe mental illness or current use of an antipsychotic medication, dementia, or evidence of substantial cognitive impairment (defined as current use of a cholinesterase inhibitor or memantine).
We randomized 150 total patients (50 patients per arm) to 1 of 3 study arms: 1) no intervention (UC); 2) an educational mailing and prescriber letter (Ed); or 3) an educational mailing, prescriber letter, and clinical pharmacist telephone counseling session (Ed+). Older adults randomized to the Ed or Ed+ study arms began receiving their intervention on January 1, 2017, and all follow-up was completed in September 2017.

The intervention was delivered as part of UC; however, because patients in the intervention arms received a signed letter from their Z-drug prescriber, some prescribers opted out of their patients receiving a letter with their signature. Patients whose prescribers opted out were not eligible to receive the intervention. To accomplish this, prescribers received an electronic medical record (EMR)-based message and had the option to opt out by responding within 14 days. Four prescribers declined to participate because they were on an extended leave (1 prescriber) or they preferred to not use a case management approach (3 prescribers).

**The Intervention**

The goal of this effort was to implement and test 2 forms of an intervention that directly provided older KPNW patients who chronically use Z-drugs with information about risks associated with Z-drug use and then engage them in shared decision making regarding discontinuation. Patients randomized to the Ed or Ed+ arms received a letter from their prescribing physician, an educational brochure, and a quiz. Educational materials were developed by a team of primary care and geriatric health care physicians, pharmacists, and researchers. Prescriber letter text explained the reason for the letter and encouraged patients to reconsider their Z-drug use. The brochure presented evidence of Z-drug-induced harms, suggestions for effective pharmacologic and nonpharmacologic alternatives to treat insomnia, and a visual tapering schedule with further instructions. The quiz reiterated messages in the educational brochure by providing a self-assessment about Z-drug use risks. A pharmacist called patients in the Ed+ study arm 2 to 4 weeks after they received the educational materials. During these telephone consultations, the pharmacist would discuss and reinforce information in the educational mailing; assess patient barriers to Z-drug discontinuation; provide personalized guidance on tapering, recommendations for care coordination opportunities available through specialty departments such as sleep medicine, mental health, and addiction medicine; and answer questions. This format also provided the opportunity to discuss Z-drug alternatives, including sleep hygiene techniques and safer medications. The pharmacist had prescriber approval and a protocol that allowed for a switch to safer sleep medications.

**Outcomes**

We followed patients for 6 months after their index date, defined as the educational material mailing date for patients in the Ed and Ed+ study arms or the first date of the intervention period for UC patients. The primary study outcome was discontinuation of Z-drugs during 6-month follow-up, defined as a patient not receiving a Z-drug dispensing from a KPNW pharmacy during that time.

We assessed occurrence of secondary outcomes, which included hospitalization, outpatient face-to-face encounters, and urgent care and Emergency Department visits during the 6-month follow-up. We also examined the number of Z-drug dispensings during follow-up for patients who did not discontinue use.

**Statistical Methods**

We used KPNW EMR data to examine baseline characteristics for patients in the UC and intervention arms. These characteristics included demographic information such as age, sex, and race; the occurrence of Charlson comorbid conditions during the year before the index date; the occurrence of insomnia or sleep disorders during the previous year; the use of psychotropic medications during the 90 days before the index date as identified through dispensings at KPNW outpatient pharmacies; and baseline health care utilization during the previous 180 days. Psychotropic drugs included anxiolytics (including benzodiazepines), antidepressants, opioids, muscle relaxants, and anticonvulsants. We identified dispensings of medications using Medi-Span Generic Product Identifiers available in KPNW EMR pharmacy data. Baseline health care utilization included hospitalization, outpatient face-to-face visits, telephone and email encounters, and urgent care and Emergency Department visits.

We identified potential imbalance in the study groups by examining standardized differences for select baseline variables. Variables with a standardized difference exceeding 0.1 between the randomized groups were considered for inclusion as control variables. Selection of potential control variables was based on plausibility of a relationship between the characteristic and Z-drug discontinuation and the prevalence of the characteristic within the population.

We compared the occurrence of discontinuation between the Ed and Ed+ groups and the UC group. Using logistic regression, we calculated crude odds ratios (ORs) and 95% confidence intervals (CIs) for discontinuation and adjusted ORs and 95% CIs that controlled for patient baseline characteristics that were imbalanced between study groups. We then described the distribution of health care utilization outcomes among study groups.

**RESULTS**

Fifty patients were randomized to each study arm and completed the intervention; however, only 49 patients from the Ed+ study arm were included in the analyses because 1 patient who received the intervention had a documented request to be excluded from research activities at KPNW. This request for exclusion does not apply to inclusion in quality improvement initiatives delivered as part of UC such as the deprescribing intervention—rather, these members are excluded from the evaluation of such initiatives.

The population was, on average, age 70 years, and most patients were women (Table 1). Thirty percent, 16%, and 18% of the UC, Ed, and Ed+ participants, respectively, had 2 or more comorbid conditions, and baseline health care utilization was low (Table 1). When we examined the use of other medications, patients most commonly received antidepressants or opioids during the prior 90 days (Table 1). Fifty-four percent of UC patients, 60% of Ed patients, and 42% of Ed+ patients had EMR documentation of insomnia. Despite randomization, there were potential imbalances among study groups with regard to age, sex, race, number
of Charlson comorbid conditions, and prior antianxiety and antidepressant medication use.

Among patients randomized to UC, 13 (26%) discontinued Z-drug use during 6 months of follow-up. Among 50 patients in the Ed arm, 28 (56%) discontinued Z-drug use, and 27 of 49 patients (55%) in the Ed+ arm discontinued Z-drug use (Table 2). The crude OR for discontinuation for the Ed arm was 3.62 (95% CI = 1.56–8.42), whereas the crude OR for the Ed+ arm was 3.49 (95% CI = 1.50–8.14; Table 2). In multivariable logistic regression controlling for age, sex, number of Charlson comorbid conditions, and prior antianxiety or antidepressant use, the odds of discontinuation were 4.02 times higher among patients who received the Ed intervention than those who received UC (adjusted OR = 4.02, 95% CI = 1.66–9.77). Patients who received the Ed+ intervention had 4.1 times greater odds of discontinuing their Z-drug use than those who received UC (adjusted OR = 4.10, 95% CI = 1.65–10.19) after controlling for baseline patient characteristics (Table 2). Patients who received an intervention but who did not discontinue Z-drug use most commonly received only 1 additional dispensing during the follow-up period (Table 3). However, those in the UC group who continued use often received 2 or more dispensings during 6-month follow-up. Consistent with the baseline, health care utilization remained low during follow-up and did not vary across patient groups (Table 3).

**DISCUSSION**

In this evaluation of a pilot deprescribing intervention, we found that patients who directly received educational materials about their Z-drug use, with or without a pharmacist consultation, were much more likely to discontinue using their drug than patients who did not receive the intervention. These results suggest that this low-resource intervention has the potential to reduce potentially harmful Z-drug effects among older adults who have a history of chronic use.

Deprescribing of potentially inappropriate medications among the elderly is an emerging area of focus for health care clinicians and health care systems, but evidence that identifies the most effective deprescribing methods is lacking. In a notable exception, the Eliminating Medications through Patient Ownership of End Results (EMPOWER) trial conducted by Marten et al and Tannenbaum et al showed that direct-to-patient education led to substantial reductions in benzodiazepine use among older adults.

### Table 1. Baseline demographic and clinical characteristics of patients in usual care, education only, and education-plus-pharmacist call intervention arms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Usual care arm (N = 50)</th>
<th>Education only arm (N = 50)</th>
<th>Education-plus-pharmacist call arm (N = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>70.7 (7.3)</td>
<td>69.9 (6.1)</td>
<td>69.4 (4.1)</td>
</tr>
<tr>
<td>Age 64 to 74 years, n (%)</td>
<td>39 (78)</td>
<td>39 (78)</td>
<td>41 (84)</td>
</tr>
<tr>
<td>Age 75 years and older, n (%)</td>
<td>11 (22)</td>
<td>11 (22)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>36 (72)</td>
<td>31 (62)</td>
<td>32 (66)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>48 (96)</td>
<td>48 (96)</td>
<td>45 (92)</td>
</tr>
<tr>
<td><strong>Charlson comorbid conditions (1 year before index date, prevalence &lt; 5%), n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>12 (24)</td>
<td>8 (16)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>10 (20)</td>
<td>6 (12)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Diabetes without chronic complications</td>
<td>4 (8)</td>
<td>6 (12)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>8 (16)</td>
<td>2 (4)</td>
<td>5 (10)</td>
</tr>
<tr>
<td><strong>Number of Charlson conditions, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27 (54)</td>
<td>29 (58)</td>
<td>31 (63)</td>
</tr>
<tr>
<td>1</td>
<td>8 (16)</td>
<td>13 (26)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>2 or more</td>
<td>15 (30)</td>
<td>8 (16)</td>
<td>9 (18)</td>
</tr>
<tr>
<td><strong>Other comorbid conditions, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>27 (54)</td>
<td>30 (60)</td>
<td>21 (43)</td>
</tr>
<tr>
<td><strong>Health care utilization (during the 180 days before the index date)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of hospitalizations, mean (SD)</td>
<td>0 (0.2)</td>
<td>0 (0.1)</td>
<td>0 (0.1)</td>
</tr>
<tr>
<td>Number of face-to-face outpatient visits, mean (SD)</td>
<td>1 (0.2)</td>
<td>0.9 (0.3)</td>
<td>0.9 (0.4)</td>
</tr>
<tr>
<td>Number of nonface-to-face outpatient visits, mean (SD)</td>
<td>1 (0.1)</td>
<td>0.9 (0.3)</td>
<td>0.9 (0.3)</td>
</tr>
<tr>
<td>Number of Urgent Care or Emergency Department visits, mean (SD)</td>
<td>0.1 (0.3)</td>
<td>0.1 (0.3)</td>
<td>0.2 (0.4)</td>
</tr>
<tr>
<td><strong>Medication use (during the 90 days before the index date, prevalence &lt; 5%), n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antianxiety medication use (yes)</td>
<td>6 (12)</td>
<td>4 (8)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Antidepressant use (yes)</td>
<td>24 (48)</td>
<td>19 (38)</td>
<td>19 (39)</td>
</tr>
<tr>
<td>Opioid use (yes)</td>
<td>21 (42)</td>
<td>14 (28)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Anticonvulsant use (yes)</td>
<td>3 (6)</td>
<td>3 (6)</td>
<td>6 (12)</td>
</tr>
</tbody>
</table>

*Includes telephone and email encounters with Kaiser Permanente Northwest practitioners. SD = standard deviation.
community-dwelling adults. A pilot study revealed that use of these educational materials was a feasible approach to initiating the deprescribing process among hospitalized individuals using sedative hypnotics.17 KPNW based its educational materials on those developed for the EMPOWER trial but modified content to discuss Z-drugs only and tailored information to be consistent with existing KPNW educational resources and practices related to sleep and tapering of Z-drug use. Our intervention also included a pharmacist telephone call for some patients. Consistent with the EMPOWER trial, our direct-to-patient education approach led to an increased likelihood of medication discontinuation. These results suggest that pharmacist contact, however, may not significantly increase discontinuation likelihood beyond the effectiveness of educational materials only. Although our findings support education as a means to deprescribing, they also point to the need for a larger study that compares education complemented by pharmacist consultation and education without the addition of a pharmacist.

This intervention addresses common concerns related to medication deprescribing among older adults. We learned about some of these concerns when we conducted a qualitative assessment of patient and primary care clinician beliefs about Z-drug deprescribing and perceptions about educational materials in parallel with pilot implementation.18 In that assessment, patients expressed the need for effective insomnia treatment and personalized approaches to care, and primary care clinicians cited a lack of insomnia treatment alternatives and institutional structures and resources to support nonbenzodiazepine medication deprescribing as barriers. There is a need to evaluate the ways in which deprescribing interventions directly address these expressed needs; however, our intervention's inclusion of information about effective alternatives to Z-drugs addressed these patient concerns. Our pharmacist consultation met the need for personalized care related to medication use. Both our educational materials and pharmacist availability represent resources that, if widely implemented, would support physicians' efforts to deprescribe harmful medications to older adults.

The intervention itself did not require a large amount of resources to implement. The educational materials were mailed by nonclinical Health Plan staff, and the telephone pharmacist consultations lasted 10 to 15 minutes. The intervention, whether implemented with or without pharmacist involvement, is a low-resource effort with great potential for reductions in harmful medication use and the poor outcomes that may be associated with that use. Furthermore, the pharmacist could switch patients to safer sleep medications when appropriate. This approach shifted case management from the prescriber to the pharmacist and probably reduced time and effort for prescribers. Although this study did not include a cost analysis, future studies that assess the cost of deprescribing interventions would increase understanding of their scope and feasibility.

This pilot study’s findings should be interpreted with limitations in mind. First, in the spirit of a pilot study, these results are based on a small population and should be interpreted as preliminary. Although formal sample size or power calculations are not required or recommended for pilot studies, we conducted calculations on the basis of the results of the EMPOWER trial and found that, with 50 patients in each arm, we had 80% power to detect a similar

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### Table 2. Logistic regression analysis of 6-month discontinuation comparing usual care to education only and education-plus-pharmacist call intervention arms

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Usual care (N = 50)</th>
<th>Education only arm (N = 50)</th>
<th>Education-plus-pharmacist call arm (N = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation (yes), n (%)</td>
<td>13 (26)</td>
<td>28 (56)</td>
<td>27 (55)</td>
</tr>
<tr>
<td>Crude OR (95% CI)</td>
<td>3.62 (1.56-6.42)</td>
<td>4.02 (1.66-9.77)</td>
<td>3.49 (1.50-8.14)</td>
</tr>
<tr>
<td>Adjusted OR (95% CI)</td>
<td>4.10 (1.65-10.19)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Calculated using logistic regression; the usual care group is the reference group. Controlling for age, sex, race, number of Charlson comorbid conditions, prior anxiety medication use, and prior antidepressant use.*

### Table 3. Secondary outcomes among usual care, education only, and education-plus-pharmacist call intervention arms

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Usual care arm (N = 50)</th>
<th>Education only arm (N = 50)</th>
<th>Education-plus-pharmacist call arm (N = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Z-drug dispensings, mean (SD)</td>
<td>1.9 (1.6)</td>
<td>1 (1.5)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Number of Z-drug dispensings by category, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 dispensings</td>
<td>13 (26)</td>
<td>28 (56)</td>
<td>27 (55)</td>
</tr>
<tr>
<td>1 dispensing</td>
<td>10 (20)</td>
<td>10 (20)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>2 dispensings</td>
<td>10 (20)</td>
<td>4 (8)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>3 dispensings</td>
<td>8 (16)</td>
<td>4 (8)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>4+ dispensings</td>
<td>9 (18)</td>
<td>4 (8)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Number of hospitalizations, mean (SD)</td>
<td>0.1 (0.2)</td>
<td>0.0 (0.2)</td>
<td>0.0 (0.1)</td>
</tr>
<tr>
<td>Number of face-to-face office visits, mean (SD)</td>
<td>0.9 (0.4)</td>
<td>0.8 (0.4)</td>
<td>0.8 (0.4)</td>
</tr>
<tr>
<td>Number of nonface-to-face encounters, mean (SD)</td>
<td>0.9 (0.3)</td>
<td>0.9 (0.3)</td>
<td>1.0 (0.0)</td>
</tr>
<tr>
<td>Number of Urgent Care or Emergency Department visits, mean (SD)</td>
<td>0.3 (0.5)</td>
<td>0.3 (0.5)</td>
<td>0.3 (0.5)</td>
</tr>
</tbody>
</table>

*Includes telephone and email encounters with Kaiser Permanente Northwest practitioners. SD = standard deviation.*
difference in discontinuation rates between each intervention group and the UC group. As a result, we could detect statistical differences; however, these results are not conclusive and point to the need for a larger trial. Furthermore, our population consisted of relatively healthy older adults who had low rates of health care utilization and a low comorbidity burden. Additional research is needed to assess the generalizability of this approach to older adults with higher comorbidity levels and more complex medical needs. In parallel, an examination of patient preference regarding potential approaches to deprescribing education such as in-person individual or group consultation would be valuable. Second, the study pharmacist was not provided with a standardized script for telephone consultations, so these interactions may not have been consistent or may be improved upon; a formalized process and additional training (eg, motivational interviewing training) may lead to improved outcomes. Third, we followed patients for 6 months, which may not be enough time to evaluate the long-term impact of the intervention on medication use. Future evaluation should examine the possibility that patients may reintiate Z-drug use after the 6-month follow-up period. Additional assessments also should evaluate substitution effects to examine whether patients are using recommended alternatives to Z-drugs or other alternatives that may not reduce risk (eg, benzodiazepines instead of Z-drugs). In turn, an examination of substitution effects should include patient use of nonpharmacologic alternatives such as cognitive behavioral therapy for insomnia. Lastly, the intervention was not delivered to patients with evidence of cognitive decline. The use of EMR data to exclude these patients may have been imperfect and could have resulted in the inclusion of patients with milder forms of cognitive decline; future studies may include these patients and evaluate outcomes among subgroups with varying levels of cognitive function. There also may be opportunities to expand the intervention to engage patient caregivers in deprescribing efforts.

CONCLUSION

Our results provide preliminary evidence that provision of evidence-based information about Z-drug use and support for discontinuation appear to increase likelihood of drug discontinuation among older adults. There is a need for research that expands the use of educational materials tailored to Z-drug deprescribing to a larger population of older adults and studies the influence of these materials over a longer time period. Future research also should assess the role of pharmacists in deprescribing and the influence of direct-to-patient education on patient-prescriber shared decision making related to Z-drug use.
**ABSTRACT**

**Context:** Cannabidiol (CBD) is one of many cannabinoid compounds found in cannabis. It does not appear to alter consciousness or trigger a “high.” A recent surge in scientific publications has found preclinical and clinical evidence documenting value for CBD in some neuropsychiatric disorders, including epilepsy, anxiety, and schizophrenia. Evidence points toward a calming effect for CBD in the central nervous system. Interest in CBD as a treatment of a wide range of disorders has exploded, yet few clinical studies of CBD exist in the psychiatric literature.

**Objective:** To determine whether CBD helps improve sleep and/or anxiety in a clinical population.

**Design:** A large retrospective case series at a psychiatric clinic involving clinical application of CBD for anxiety and sleep complaints as an adjunct to usual treatment. The retrospective chart review included monthly documentation of anxiety and sleep quality in 103 adult patients.

**Main Outcome Measures:** Sleep and anxiety scores, using validated instruments, at baseline and after CBD treatment.

**Results:** The final sample consisted of 72 adults presenting with primary concerns of anxiety (n = 47) or poor sleep (n = 25). Anxiety scores decreased within the first month in 57 patients (79.2%) and remained decreased during the study duration. Sleep scores improved within the first month in 48 patients (66.7%) but fluctuated over time. In this chart review, CBD was well tolerated in all but 3 patients.

**Conclusion:** Cannabidiol may hold benefit for anxiety-related disorders. Controlled clinical studies are needed.

**INTRODUCTION**

The *Cannabis* plant has been cultivated and used for its medicinal and industrial benefits dating back to ancient times. *Cannabis sativa* and *Cannabis indica* are the 2 main species. The *Cannabis* plant contains more than 80 different chemicals known as cannabinoids. The most abundant cannabinoid, tetrahydrocannabinol (THC), is well known for its psychoactive properties, whereas cannabidiol (CBD) is the second-most abundant and is nonpsychoactive. Different strains of the plant are grown containing varying amounts of THC and CBD. Hemp plants are grown for their fibers and high levels of CBD that can be extracted to make oil, but marijuana plants grown for recreational use have higher concentrations of THC compared with CBD. Industrial hemp must contain less than 0.3% THC to be considered legal, and it is from this plant that CBD oil is extracted.

Many different cultures have used the *Cannabis* plant to treat a plethora of ailments. Practitioners in ancient China targeted malaria, menstrual symptoms, gout, and constipation. During medieval times, cannabis was used for pain, epilepsy, nausea, and vomiting, and in Western medicine it was commonly used as an analgesic. In the US, physicians prescribed *Cannabis sativa* for a multitude of illnesses until restrictions were put in place in the 1930s and then finally stopped using it in 1970 when the federal government listed marijuana as a Schedule I substance, claiming it an illegal substance with no medical value. California was the first state to go against the federal ban and legalize medical marijuana in 1996. As of June 2018, 9 states and Washington, DC, have legalized recreational marijuana, and 30 states and Washington, DC, allow for use of medical marijuana. The purpose of the present study is to describe the effects of CBD on anxiety and sleep among patients in a clinic presenting with anxiety or sleep as a primary concern.

CBD has demonstrated preliminary efficacy for a range of physical and mental health care problems. In the decade before 2012, there were only 9 published studies on the use of cannabinoids for medicinal treatment of pain; since then, 30 articles have been published on this topic, according to a PubMed search conducted in December 2017. Most notable was a study conducted at the University of California, San Diego’s Center for Medicinal Cannabis Research that showed cannabis cigarettes reduced pain by 34% to 40% compared with placebo (17% to 20% decrease in pain). In particular, CBD appears to hold benefits for a wide range of neurologic disorders, including decreasing major seizures. A recent large, well-controlled study of pediatric epilepsy documented a beneficial effect of CBD in reducing seizure frequency by more than 50%. In addition to endorphin release, the “runner’s high” experience after exercise has been shown to be induced in part by anandamide acting on CB1 receptors, eliciting anxiolytic effects on the body. The activity of CBD at 5-HT1A receptors may drive its neuroprotective, antidepressive, and anxiolytic benefits, although the mechanism of action by which CBD decreases anxiety is still unclear. CBD was shown to be helpful for decreasing anxiety through a simulated public speaking test at doses of 300 mg to 600 mg in single-dose studies. Other studies suggest lower doses of 10 mg/kg having a more anxiolytic effect than higher doses of 100 mg/kg in rats. A crossover study comparing CBD with nitrazepam found that high-dose CBD at 160 mg increased the duration of sleep. Another crossover study showed that...
plasma cortisol levels decreased more significantly when given oral CBD, 300 to 600 mg, but these patients experienced a sedative effect.17 The higher doses of CBD that studies suggest are therapeutic for anxiety, insomnia, and epilepsy may also increase mental sedation.18 Administration of CBD via different routes and long-term use of 10 mg/d to 400 mg/d did not create a toxic effect on patients. Doses up to 1500 mg/d have been well tolerated in the literature.19 Most of the research done has been in animal models and has shown potential benefit, but clinical data from randomized controlled experiments remain limited.

Finally, the most notable benefit of cannabis as a form of treatment is safety. There have been no reports of lethal overdose with either of the cannabinoids and, outside of concerns over abuse, major complications are very limited.19 Current research indicates that cannabis has a low overall risk with short-term use, but more research is needed to clarify possible long-term risks and harms.

Given the promising biochemical, physiologic, and preclinical data on CBD, a remarkable lack of randomized clinical trials and other formal clinical studies exist in the psychiatric arena. The present study describes a series of patients using CBD for treatment of anxiety or sleep disturbances in a clinical practice setting. Given the paucity of data in this area, clinical observations can be quite useful to advance the knowledge base and to offer questions for further investigation. This study aimed to determine whether CBD is helpful for improving sleep and/or anxiety in a clinical population. Given the novel nature of this treatment, our study also focused on tolerability and safety concerns. As a part of the evolving legal status of cannabis, our investigation also looked at patient acceptance.

METHODS
Design and Procedures
A retrospective chart review was conducted of adult psychiatric patients with CBD for anxiety or sleep as an adjunct to treatment as usual at a large psychiatric outpatient clinic. Any current psychiatric patient with a diagnosis by a mental health professional (psychiatrist, psychiatric nurse practitioner, or physician assistant) of a sleep or anxiety disorder was considered. Diagnosis was made by clinical evaluation followed by baseline psychologic measures. These measures were repeated monthly. Comorbid psychiatric illnesses were not a basis for exclusion. Additionally, other psychiatric medications were administered as per routine patient care. Selection for the case series was contingent on informed consent to be treated with CBD for 1 of these 2 disorders and at least 1 month of active treatment with CBD. Patients treated with CBD were provided with psychiatric care and medications as usual. Most patients continued to receive their psychiatric medications. The patient population mirrored the clinic population at large with the exception that it was younger.

Nearly all patients were given CBD 25 mg/d in capsule form. If anxiety complaints predominated, the dosing was every morning, after breakfast. If sleep complaints predominated, the dosing was every evening, after dinner. A handful of patients were given CBD 50 mg/d or 75 mg/d. One patient with a trauma history and schizoaffective disorder received a CBD dosage that was gradually increased to 175 mg/d.

Often CBD was employed as a method to avoid or to reduce psychiatric medications. The CBD selection and dosing reflected the individual practitioner’s clinical preference. Informed consent was obtained for each patient who was treated and considered for this study. Monthly visits included clinical evaluation and documentation of patients’ anxiety and sleep status using validated measures. CBD was added to care, dropped from care, or refused as per individual patient and practitioner preference. The Western Institutional Review Board, Puyallup, WA, approved this retrospective chart review.

Setting and Sample
Wholeness Center is a large mental health clinic in Fort Collins, CO, that focuses on integrative medicine and psychiatry. Practitioners from a range of disciplines (psychiatry, naturopathy, acupuncture, neurofeedback, yoga, etc) work together in a collaborative and cross-disciplinary environment. CBD had been widely incorporated into clinical care at Wholeness Center a few years before this study, on the basis of existing research and patient experience.

The sampling frame consisted of 103 adult patients who were consecutively treated with CBD at our psychiatric outpatient clinic. Eighty-two (79.6%) of the 103 adult patients had a documented anxiety or sleep disorder diagnosis. Patients with sole or primary diagnoses of schizophrenia, posttraumatic stress disorder, and agitated depression were excluded. Ten patients were further excluded because they had only 1 documented visit, with no follow-up assessment. The final sample consisted of 72 adult patients presenting with primary concerns of anxiety (65.3%; n = 47) or poor sleep (34.7%; n = 25) and who had at least 1 follow-up visit after CBD was prescribed.

Main Outcome Measures
Sleep and anxiety were the targets of this descriptive report. Sleep concerns were tracked at monthly visits using the Pittsburg Sleep Quality Index. Anxiety levels were monitored at monthly visits using the Hamilton Anxiety Rating Scale. Both scales are nonproprietary. The Hamilton Anxiety Rating Scale is a widely used and validated anxiety measure with 14 individual questions. It was first used in 1959 and covers a wide range of anxiety-related concerns. The score ranges from 0 to 56. A score under 17 indicates mild anxiety, and a score above 25 indicates severe anxiety. The Pittsburg Sleep Quality Index is a self-report measure that assesses the quality of sleep during a 1-month period. It consists of 19 items that have been found to be reliable and valid in the assessment of a range of sleep-related problems. Each item is rated 0 to 3 and yields a total score from 0 to 21. A higher number indicates more sleep-related concerns. A score of 5 or greater indicates a “poor sleeper.”
Side effects and tolerability of CBD treatment were assessed through spontaneous patient self-reports and were documented in case records. Any other spontaneous comments or complaints of patients were also documented in case records and included in this analysis.

Data Analysis
Deidentified patient data were evaluated using descriptive statistics and plotted graphically for visual analysis and interpretation of trends.

RESULTS
The average age for patients with anxiety was 34 years (range = 18–70 years) and age 36.5 years for patients with sleep disorders (range = 18–72 years). Most patients with an anxiety diagnosis were men (59.6%, 28/47), whereas more sleep-disordered patients were women (64.0%, 16/25). All 72 patients completed sleep and anxiety assessments at the onset of CBD treatment and at the first monthly follow-up. By the second monthly follow-up, 41 patients (56.9%) remained on CBD treatment and completed assessments; 27 patients (37.5%) remained on CBD treatment at the third monthly assessment.

Table 1 provides means and standard deviations for sleep and anxiety scores at baseline and during the follow-up period for adults taking CBD. Figure 1 graphically displays the trend in anxiety and sleep scores over the study period. On average, anxiety and sleep improved for most patients, and these improvements were sustained over time. At the first monthly assessment after the start of CBD treatment, 79.2% (57/72) and 66.7% (48/72) of all patients experienced an improvement in anxiety and sleep, respectively; 15.3% (11/72) and 25.0% (18/72) experienced worsening symptoms in anxiety and sleep, respectively. Two months after the start of CBD treatment, 78.1% (32/41) and 56.1% (23/41) of patients reported improvement in anxiety and sleep, respectively, compared with the prior monthly visit; again, 19.5% (8/41) and 26.8% (11/41), respectively, reported worsening problems as compared with the prior month.

Table 1. Descriptive statistics for anxiety and sleep scores among adults using cannabidiol treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HAM-A, mean (SD)</th>
<th>PSQI, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety (n = 47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>23.87 (9.87)</td>
<td>10.98 (3.43)</td>
</tr>
<tr>
<td>1-month follow-up</td>
<td>18.02 (7.56)</td>
<td>8.88 (3.68)</td>
</tr>
<tr>
<td>2-month follow-up</td>
<td>16.35 (8.80)</td>
<td>8.59 (2.91)</td>
</tr>
<tr>
<td>3-month follow-up</td>
<td>16.36 (9.80)</td>
<td>9.25 (2.46)</td>
</tr>
<tr>
<td>Sleep disorder (n = 25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>22.18 (7.55)</td>
<td>13.08 (3.03)</td>
</tr>
<tr>
<td>1-month follow-up</td>
<td>17.82 (9.72)</td>
<td>10.64 (3.89)</td>
</tr>
<tr>
<td>2-month follow-up</td>
<td>17.36 (10.91)</td>
<td>9.39 (3.81)</td>
</tr>
<tr>
<td>3-month follow-up</td>
<td>13.78 (7.86)</td>
<td>9.33 (4.63)</td>
</tr>
</tbody>
</table>

HAM-A = Hamilton Anxiety Rating Scale; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation.

Figure 1. Mean anxiety and sleep scores for adults using cannabidiol treatment. HAM-A = Hamilton Anxiety Rating Scale; PSQI = Pittsburgh Sleep Quality Index.

These results demonstrated a more sustained response to anxiety than for sleep over time. Patient records displayed a larger decrease in anxiety scores than in sleep scores. The sleep scores demonstrated mild improvement. The anxiety scores decreased within the first month and then remained decreased during the study duration.

CBD was well tolerated, with few patients reporting side effects. Two patients discontinued treatment within the first week because of fatigue. Three patients noted mild sedation initially that appeared to abate in the first few weeks. One patient with a developmental disorder (aged 21 years) had to be taken off the CBD regimen because of increased sexually inappropriate behavior. The CBD was held, and the behavior disappeared. The behavior reappeared on redosing 2 weeks later, and the CBD regimen was formally discontinued. The treating psychiatrist thought this was related to disinhibition because the patient’s anxiety responded dramatically. One patient noted dry eyes. Reasons for patients not following-up at later assessment points are largely unknown but are probably because of standard attrition experienced in usual clinical practice. There was no evidence to suggest patients discontinued care because of tolerability concerns. The attrition rates were similar in nature and size to those found in routinely scheduled visits in this clinic.

The treatment with CBD was in general well accepted, as judged by the clinicians’ and patients’ responses. Four patients declined CBD treatment because of religious or ethical concerns about the relation to cannabis. Nearly all patients easily provided informed consent once the nature of the treatment was explained. Most patients appreciated the opportunity to try something natural and avoid further or initial psychiatric medication use.

DISCUSSION
In an outpatient psychiatric population, sleep scores displayed no sustained improvements during the 3-month study. Anxiety scores decreased fairly rapidly, and this decrease was sustained during the study period. These results are consistent with the existing preclinical and clinical data on CBD. CBD was well accepted and well tolerated in our patients. Side effects were minimal (mainly fatigue) and may be related to dosing.
The doses used in this study (25 mg/d to 175 mg/d) were much lower than those reported in some of the clinical literature (300 mg/d to 600 mg/d) for 2 reasons. The first is that in our experience lower doses appear to elicit an adequate clinical response. Second, the current retail cost of CBD would make the use of 600 mg/d cost prohibitive.

Study Limitations

These results must be interpreted cautiously because this was a naturalistic study, all patients were receiving open-label treatment, and there was no comparison group. Concurrent psychiatric medications were employed as in routine clinical care. This is both a limitation and strength, as very few publications exist in this population. Other researchers have noted that the large societal notoriety about cannabis and medical marijuana probably contributes to a larger-than-normal placebo effect. Any study that explores efficacy in this therapy probably will struggle with a potentially inflated placebo effect that will make these determinations more difficult. Likewise, the clinical population in this case series is skewed younger than typical for our clinic, and future studies could explore the possible selection bias inherent in this treatment option. Most patients were also taking psychiatric medications and receiving other mental health services, such as counseling, which limits the ability to make any causal links to CBD treatment. Clinical attrition is evident in the dataset. The reason for this might be related to CBD ingestion or not, so the overall component remains unclear. Furthermore, patients at our clinic often express a desire to reduce or to avoid use of psychiatric medications, which may contribute to an enhanced placebo effect or additional bias. The length of clinical monitoring may help to decrease this concern. However, the clinical data in this analysis show a trend toward clinically significant relief of anxiety upon the start of CBD treatment.

Legality of Cannabidiol

The legality of CBD is not clear. Like the issues surrounding the legality of cannabis in general, CBD presents the clinician with a confusing state vs federal legal quandary, and this keeps the issue in question. CBD is legal in the 33 states that have legalized medical or recreational use of marijuana and in 17 other states that have legalized some form of CBD, according to the National Organization for the Reform of Marijuana Laws (NORML). But like marijuana, it is still not legal at the federal level. The federal government has announced that it is not focused on this compound in terms of enforcement or interdiction. However, CBD is interpreted by the Drug Enforcement Administration, Food and Drug Administration, and Congress to be a Schedule I substance, and therefore it is illegal in all 50 states. Pragmatically, CBD is widely available on the Internet, with sales expected to reach $1 billion by 2020. Pending federal legislation to redefine the legal status of cannabis would clarify this complex issue. Canada’s move to legalize cannabis in October 2018 further highlights the need for a speedy resolution to this question.

CONCLUSION

Formal studies on efficacy and dose finding are much needed. Some urgency exists, given the explosion of lay interest in this topic and the rush to market these compounds. Current understanding of the physiology and neurologic pathways points to a benefit with anxiety–related issues. The results of our clinical report support the existing scientific evidence. In our study, we saw no evidence of a safety issue that would limit future studies. In this evaluation, CBD appears to be better tolerated than routine psychiatric medications. Furthermore, CBD displays promise as a tool for reducing anxiety in clinical populations, but given the open-label and nonrandomized nature of this large case series, all results must be interpreted very cautiously. Randomized and controlled trials are needed to provide definitive clinical guidance.

Disclosure Statement

Dr Shannon has published several professional books on integrative mental health. Dr Shannon is a Principal Investigator for a Phase 3 study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for severe posttraumatic stress disorder and receives compensation for his clinical work from the Multidisciplinary Association for Psychedelic Studies, Santa Cruz, CA. The other authors have no conflicts of interests to disclose.

Acknowledgments

CV Sciences Inc, Las Vegas, NV, provided cannabidiol products for the study. CV Sciences was not involved in the data collection, data interpretation, preparation of the report, or decision to submit the report for publication. No other financial support was provided. The authors would like to express their deep appreciation to the staff and clinicians at Wholeness Center for their professionalism.

Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

How to Cite this Article


References


Influence

The psychological effects of cannabinoids, such as anxiety reduction, sedation, and euphoria can influence their potential therapeutic value.

ORIGINAL RESEARCH & CONTRIBUTIONS

Gabapentin and Cancer Risk: Updated Findings from Kaiser Permanente Northern California

Gary D Friedman, MD, MS1,2; Ninah Achacoso, MS1; Laurel A Habel, PhD1

ABSTRACT

Context: Epidemiologic analyses of gabapentin use and cancer risk in Kaiser Permanente Northern California were previously carried out in a collaborative study and independently evaluated in a UK database.

Objective: To update these epidemiologic analyses with 7.5 more years of follow-up.

Design: Case-control analyses using conditional logistic regression to estimate relative risk by odds ratios using the prior collaboration’s criteria for identifying positive drug-cancer associations and our more stringent criteria requiring stronger association, lower p values, and evidence of dose response. New associations were reanalyzed with additional control for limited measures of smoking and alcohol use.

Main Outcome Measures: Gabapentin-cancer associations.

Results: No previously found associations met our stringent criteria, but cancers of the mouth/pharynx, esophagus, liver, and vagina did. All odds ratios for 3 or more and 8 or more prescriptions were moderately reduced by control for smoking and alcohol. Substantial elevations of risk of mouth/pharynx, liver, and vaginal cancers were associated with only 1 prescription dispensed. Sensitivity analyses aimed at possible confounding and other biases did not change our conclusions but did reveal a markedly increased risk of vaginal cancer in gabapentin users with epilepsy compared with users without.

Conclusion: The reduced magnitude of relative risk with control for smoking and alcohol use suggests confounding by known risk factors. Biologically implausible elevated risk from just 1 prescription suggests confounding by indication. Either or both of these concerns applies to each of the 4 cancer sites associated with gabapentin use. Updated analyses show little if any evidence for carcinogenic effects of gabapentin.

INTRODUCTION

In 2011, we participated in a collaborative study, headed by Michael Irizarry, MD, MPH, of GlaxoSmithKline Corporation, Research Triangle Park, NC, regarding the relation of gabapentin use to the risk of cancer development.1 High doses of gabapentin, an anticonvulsive and analgesic pharmaceutical drug, had been found to be associated with the development of pancreatic acinar cell tumors in male Wistar rats,2 which prompted that study.

For that study, our previous case-control screening of pharmaceuticals for possible carcinogenicity in Kaiser Permanente Northern California (KPNC)3 was used to identify possible gabapentin-cancer associations in humans, which were independently evaluated in the UK General Practice Research Database (GPRD).4 This computerized database, now called the Clinical Practice Research Datalink, contained anonymized data from patient records in the UK collected since 1987. Compared with no dispensings, 3 or more dispensings of gabapentin were minimally associated (odds ratio [OR] > 1.0, p < 0.05) with 9 cancer sites in KPNC members. These cancers were of the breast, lung/bronchus, urinary bladder, kidney/renal pelvis, stomach, anus/anal canal/anorectum, penis, other nervous system, and any cancer.1 Only 1 of these, kidney/renal pelvis cancer, would meet our stricter screening criteria for limiting false-positive results (OR ≥ 1.50, p ≤ 0.01, higher risk for ≥ 3 dispensings than for 1 dispensing), suggesting dose response.1 We suggested that this was subject to likely confounding by cigarette smoking and hypertension, but this possibility was not confirmed in additional analyses. There were 2 statistically significant associations in the GPRD analyses: Pancreatic cancer and renal cancer, but for both cancer sites there was no evidence of dose response or evidence for protopathic bias (prescribed for symptoms of cancer before diagnosis).

We now have 7.5 more years of follow-up data (January 2007-June 2014) for cancer occurrence and conducted the present study of gabapentin solely within KPNC and completely independent of the previous collaborating investigators. Our goals were to reevaluate previous associations and evaluate those newly found.

METHODS

As approved by the institutional review board of the Kaiser Foundation Research Institute, we have screened pharmaceutical drugs for possible carcinogenic effects in a research database of KPNC, an integrated health care system that currently has approximately 4 million subscribers. Data include records of prescriptions dispensed from KPNC pharmacies, clinical and laboratory data, and a cancer registry that reports to the California Cancer Registry and the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program.4 Case-control analyses using conditional logistic regression are conducted in a cohort of subscribers with at least partial coverage of prescription costs and with membership starting on or after January 1, 1996, and followed-up until they left membership for any reason or June 30, 2014, whichever came first. Almost 100% of this cohort obtained all their prescriptions from KPNC pharmacies.5 The earlier collaborative study6 also encompassed pharmacy records from August 1, 1994, through December 31, 1995, which were not included.

Keywords: cancer risk, carcinogenesis, carcinogen, gabapentin, neoplasms

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in the newer research database. Up to 50 individuals without cancer (controls) are selected for each patient with cancer (case) and matched for age, sex, and year that KPNC membership began. The index date is the date of diagnosis for cases and the same or nearby date for controls that gives them equal follow-back time for ascertainment of drug exposure. Because of their increased risk of several cancers, patients who are positive for HIV infection were excluded from the study cohort. All analyses exclude subjects with previous cancers at any cancer site, include a 2-year lag (ignore prescriptions within the 2 years before the index date), and are controlled for race/ethnicity.

For the previous collaborative study, gabapentin–cancer associations were identified simply if the OR was greater than 1.0 and \( p < 0.05 \). Although the 2-year medication lag was used, there was no control for race/ethnicity, and HIV-positive subjects were excluded only in the analysis of cancer of the anus/anal canal/anorectum. The 9 cancer sites that met these criteria (listed in the Introduction) were analyzed again using the same criteria. We also screened all 56 cancer sites using our more stringent criteria (OR ≥ 1.50, p ≤ 0.01, higher risk for ≥ 3 prescriptions than for 1 prescription as an indication of dose-response). Because the 4 cancer sites that previously screened positive have cigarette smoking and alcohol use as established risk factors—mouth/pharynx, esophagus, liver, and vagina (alcohol use possible)—we conducted multivariable analyses adding these 2 variables to the models. On the basis of oral and written questionnaires used in clinical encounters (using the earliest available record), cigarette smoking was classified as current, former, unknown, and never (reference), and alcohol use was classified as unknown, used less than 3 drinks per day, used 3 or more drinks per day, used unknown amount, and none (reference).

We conducted several sensitivity analyses to examine other potential confounding or biasing factors. These included controlling for socioeconomic status (using 2 available measures: Census block of residence and educational level); omitting alcohol use from the multivariable model because of incompleteness of the data; controlling for use vs nonuse of other

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>No. of gabapentin-exposed cases, previous/latest</th>
<th>Previous OR (95% CI)a</th>
<th>Latest OR (95% CI)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>352/628</td>
<td>1.19 (1.01-1.39)</td>
<td>1.02 (0.94-1.10)</td>
</tr>
<tr>
<td>Lung/bronchus</td>
<td>269/517</td>
<td>1.34 (1.13-1.60)</td>
<td>1.36 (1.24-1.48)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>100/173</td>
<td>1.41 (1.07-1.87)</td>
<td>1.15 (0.99-1.34)</td>
</tr>
<tr>
<td>Kidney/renal pelvis</td>
<td>70/134</td>
<td>1.71 (1.18-2.47)</td>
<td>1.44 (1.21-1.72)</td>
</tr>
<tr>
<td>Stomach</td>
<td>27/58</td>
<td>1.64 (1.01-2.64)</td>
<td>1.28 (0.98-1.67)</td>
</tr>
<tr>
<td>Anus/anal canal/anorectum</td>
<td>9/20</td>
<td>2.70 (1.16-6.25)</td>
<td>1.48 (0.94-2.34)</td>
</tr>
<tr>
<td>Penis</td>
<td>3/5</td>
<td>6.68 (1.47-30.28)</td>
<td>3.43 (1.33-8.85)</td>
</tr>
<tr>
<td>Other nervous system</td>
<td>2/2</td>
<td>6.67 (1.11-39.90)</td>
<td>1.53 (0.36-6.50)</td>
</tr>
<tr>
<td>Any cancer</td>
<td>1678/3662</td>
<td>1.10 (1.02-1.18)</td>
<td>1.08 (1.04-1.11)</td>
</tr>
</tbody>
</table>

a Odds ratio > 1.0, \( p < 0.05 \).

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>No. of gabapentin-exposed cases, previous/latest</th>
<th>Previous OR (95% CI)a</th>
<th>Latest OR (95% CI)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth/pharynx</td>
<td>3670</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Only 1</td>
<td>52</td>
<td>1.37 (1.03-1.81)</td>
<td>1.26 (0.95-1.67)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>86</td>
<td>1.62 (1.30-2.02)</td>
<td>1.48 (1.18-1.85)</td>
</tr>
<tr>
<td>≥ 8</td>
<td>38</td>
<td>1.41 (1.02-1.96)</td>
<td>1.26 (0.91-1.76)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1601</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Only 1</td>
<td>152</td>
<td>1.14 (0.75-1.74)</td>
<td>1.05 (0.69-1.61)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>45</td>
<td>1.59 (1.18-2.16)</td>
<td>1.39 (1.02-1.89)</td>
</tr>
<tr>
<td>≥ 8</td>
<td>35</td>
<td>2.53 (1.78-3.58)</td>
<td>2.15 (1.51-3.07)</td>
</tr>
<tr>
<td>Liver</td>
<td>2877</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Only 1</td>
<td>57</td>
<td>1.56 (1.19-2.05)</td>
<td>1.38 (1.05-1.81)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>90</td>
<td>1.97 (1.59-2.45)</td>
<td>1.64 (1.32-2.05)</td>
</tr>
<tr>
<td>≥ 8</td>
<td>40</td>
<td>1.82 (1.32-2.50)</td>
<td>1.45 (1.05-2.01)</td>
</tr>
<tr>
<td>Vagina</td>
<td>139</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Only 1</td>
<td>126</td>
<td>3.22 (1.27-8.20)</td>
<td>3.04 (1.19-7.76)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>8</td>
<td>3.35 (1.57-7.16)</td>
<td>3.01 (1.40-6.48)</td>
</tr>
<tr>
<td>≥ 8</td>
<td>6</td>
<td>4.70 (1.96-11.28)</td>
<td>4.08 (1.67-9.93)</td>
</tr>
</tbody>
</table>

a Risk estimated by ORs listed according to the number of prescriptions dispensed. Note that ≥ 3 prescriptions includes ≥ 8 prescriptions.

a Adjusted for race/ethnicity.

a Adjusted for race/ethnicity, smoker status, and alcohol use. Two-year lag.

CI = confidence interval; KPNC = Kaiser Permanente Northern California; OR = odds ratio.
antiepileptic drugs; analyzing users of gabapentin with epilepsy (ascertained by clinical diagnosis or receipt of antiepileptic drugs) separately from other users of gabapentin, many of whom probably received it to control pain; analyzing by cumulative dose received rather than the number of prescriptions; and changing 2-year lag to no lag to include all prescriptions received up to the index date.

RESULTS
Reanalysis using the original weak criteria with 7.5 additional years of follow-up yielded reduced ORs and loss of statistical significance for cancers of the breast, urinary bladder, stomach, anal/anal canal/anorectum, and other nervous system. Cancers of the kidney/renal pelvis and the penis had lower but still statistically significant ORs with longer follow-up, and associations with lung cancer and all cancers combined showed very little change and remained significant (Table 1).

Findings with New Screening Criteria
None of the original 9 cancer sites met our more stringent screening criteria. Four other cancer sites did: Mouth/pharynx, esophagus, liver, and vagina. Table 2 shows the initial screening findings (Model 1) and multivariable analyses with cigarette smoking and alcohol use added (Model 2). Displayed are the main results: ORs for only 1 prescription, 3 or more prescriptions, and 8 or more prescriptions (included in ≥ 3 prescriptions) of gabapentin. ORs for mouth/pharynx were mildly elevated, with some evidence of dose response, when we compared 3 or more prescriptions with 1 prescription but not 8 or more prescriptions with 1 prescription. Adjustment for cigarette smoking and alcohol use reduced all ORs moderately. Esophageal cancer showed clearly elevated and statistically significant ORs for 3 or more and 8 or more prescriptions, with evidence of dose response, and moderate reductions in risk with control for cigarette smoking and alcohol use. Associations with liver cancer were all statistically significant, even with only 1 prescription. After adjustment for cigarette smoking and alcohol use, which reduced ORs moderately, dose response was suggested in a comparison of 3 or more but not 8 or more prescriptions with 1 prescription. ORs, including that for only 1 prescriptions, were all greater than 3.0 for vaginal cancer despite small

<table>
<thead>
<tr>
<th>Table 3. Sensitivity analyses: Results of modified multivariable analyses compared with original model for relative risk of cancer at 4 sites that screened positive for association with gabapentin use*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of prescriptions by cancer site</strong></td>
</tr>
<tr>
<td><strong>Mouth/pharynx</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Only 1</td>
</tr>
<tr>
<td>≥ 3</td>
</tr>
<tr>
<td>≥ 8</td>
</tr>
<tr>
<td><strong>Esophagus</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Only 1</td>
</tr>
<tr>
<td>≥ 3</td>
</tr>
<tr>
<td>≥ 8</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Only 1</td>
</tr>
<tr>
<td>≥ 3</td>
</tr>
<tr>
<td>≥ 8</td>
</tr>
<tr>
<td><strong>Vagina</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Only 1</td>
</tr>
<tr>
<td>≥ 3</td>
</tr>
<tr>
<td>≥ 8</td>
</tr>
</tbody>
</table>

* Risk estimated by odds ratios (and 95% confidence intervals) listed according to the number of prescriptions dispensed. Note that ≥ 3 prescriptions includes ≥ 8 prescriptions.

All with 2-year lag except where indicated. Original model was adjusted for race/ethnicity, smoking status, and alcohol use.

*Adjusted for race/ethnicity, smoking status, alcohol use, and use vs nonuse of other antiepileptic drugs.

*Adjusted for race/ethnicity, smoking status, alcohol use, and gabapentin users classified to those with an epilepsy diagnosis or other antiepileptic drug use and those without an epilepsy diagnosis and without use of other antiepileptic drugs.

*Adjusted for race/ethnicity, smoking status, and alcohol use. Two-year lag eliminated.
numbers of cases with gabapentin use. As with the other cancer sites, adjustment for cigarette smoking and alcohol use reduced ORs moderately.

The full models with results for 1, 2, 3, 4 to 7, and 8 or more prescriptions and for all categories of race/ethnicity, cigarette smoking, and alcohol use in relation to the risk of each of the 4 cancers are provided as Supplemental Tables 1 to 4, available at www.thepermanentejournal.org/files/2018/18-040-Suppl.pdf.

Although the previous collaborative study was prompted mainly by experimental evidence of an association of gabapentin use with pancreatic cancer in rats,\textsuperscript{2} we again found no statistically significant association of gabapentin with this cancer site; the OR for 3 or more prescriptions vs none was 1.15 (95% confidence interval [CI] = 0.95–1.40) based on 109 cases and 4634 controls. One cancer site, rectum/rectosigmoid, met our analogous strict screening criteria for a negative association OR less than 0.67 for 3 or more prescriptions vs none and more negative than the OR for 1 prescription vs none. The findings for this cancer site were as follows: 3 or more vs 0 prescriptions: OR = 0.61 (95% CI = 0.46–0.82) based on 46 cases and 3650 controls; 1 vs 0 prescriptions: OR = 1.01 (95 CI = 0.78–1.31) based on 58 cases and 2782 controls. This negative association was not evaluated further.

**Sensitivity Analyses**

The addition of indicators related to socioeconomic status yielded ORs virtually identical to those absent of this change (Table 3). Exclusion of alcohol use from the model resulted in slightly higher ORs for all number-of-prescription categories for all 4 cancer sites (Table 3). The opposite was true when use vs nonuse of other antiepileptic drugs was added to the model, with slight decreases in all number-of-prescription categories for all 4 cancer sites (Table 3).

About 30% of gabapentin–using cases had a diagnosis of epilepsy or used another drug for treatment of epilepsy. For example, of the 154 gabapentin recipients among cases of the most frequent cancer site, mouth/pharynx, 49 (31.8%) had a diagnosis or other drug for epilepsy (epilepsy subgroup), and 105 (68.2%) did not (nonepilepsy subgroup). These 2 subgroups of gabapentin users were entered separately into the multivariable analysis. For mouth/pharynx cancer, ORs were somewhat lower in the epilepsy subgroup than in the nonepilepsy subgroup for only 1 and for 8 or more prescriptions. This was also the case for 3 or more and 8 or more prescriptions in relation to esophageal cancer and for all 3 prescription categories in relation to liver cancer.

Regarding vaginal cancer, the subgroups differed markedly. The nonepilepsy subgroup showed no statistically significant increases in risk and the users of only 1 prescription had the highest OR, 1.76 (95% CI = 0.4 2–7.34). The smaller subgroup, those with epilepsy, had high and statistically significant ORs ranging from 6.21 (95% CI = 1.77–21.78) for only 1 prescription to 7.91 (95% CI = 2.91–21.48) for ≥ 8 prescriptions. Because of small numbers, all CIs were wide, and there was considerable overlap of the CIs between the epilepsy and nonepilepsy subgroups, reducing confidence that they truly differ (Table 3).

ORs from the multivariable analysis by cumulative dose (Table 4, Model 2) are best compared with multivariable analysis by number of prescriptions (Table 2, Model 2), both controlled for cigarette

---

### Table 4. Sensitivity analyses based on cumulative dose: Relative risk of cancer at 4 sites that screened positive for association with gabapentin use\textsuperscript{a}

<table>
<thead>
<tr>
<th>Cumulative dose (in grams)</th>
<th>Cases, no.</th>
<th>Controls, no.</th>
<th>Model 1\textsuperscript{b}</th>
<th>Model 2\textsuperscript{c}</th>
<th>Model 3\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mouth/pharynx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3670</td>
<td>182,423</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>0</td>
<td>3516</td>
<td>177,248</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>&gt; 0 to &lt; 30</td>
<td>30</td>
<td>1250</td>
<td>1.18 (0.82–1.70)</td>
<td>1.12 (0.77–1.61)</td>
<td>1.02 (0.74–1.41)</td>
</tr>
<tr>
<td>30 to &lt; 60</td>
<td>26</td>
<td>1057</td>
<td>1.22 (0.82–1.80)</td>
<td>1.10 (0.75–1.64)</td>
<td>1.27 (0.93–1.73)</td>
</tr>
<tr>
<td>60 to &lt; 150</td>
<td>35</td>
<td>1057</td>
<td>1.81 (1.15–2.73)</td>
<td>1.48 (1.05–2.08)</td>
<td>1.36 (1.03–1.82)</td>
</tr>
<tr>
<td>≥ 150</td>
<td>63</td>
<td>1811</td>
<td>1.65 (1.27–2.13)</td>
<td>1.49 (1.15–1.93)</td>
<td>1.49 (1.20–1.84)</td>
</tr>
<tr>
<td><strong>Esophagus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1601</td>
<td>79,534</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
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<tr>
<td>0</td>
<td>1524</td>
<td>76,746</td>
<td>0.97 (0.56–1.89)</td>
<td>0.89 (0.51–1.55)</td>
<td>0.96 (0.61–1.53)</td>
</tr>
<tr>
<td>&gt; 0 to &lt; 30</td>
<td>13</td>
<td>683</td>
<td>1.06 (0.58–1.94)</td>
<td>1.00 (0.55–1.83)</td>
<td>1.14 (0.71–1.83)</td>
</tr>
<tr>
<td>30 to &lt; 60</td>
<td>11</td>
<td>521</td>
<td>1.55 (0.97–2.49)</td>
<td>1.34 (0.83–2.17)</td>
<td>1.19 (0.78–1.81)</td>
</tr>
<tr>
<td>60 to &lt; 150</td>
<td>18</td>
<td>582</td>
<td>1.94 (1.40–2.66)</td>
<td>1.74 (1.26–2.42)</td>
<td>1.53 (1.15–2.02)</td>
</tr>
<tr>
<td>≥ 150</td>
<td>35</td>
<td>1022</td>
<td>1.68 (1.19–2.37)</td>
<td>1.44 (1.02–2.04)</td>
<td>1.36 (1.01–1.84)</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2877</td>
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<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
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<td>137,729</td>
<td>1.74 (1.27–2.39)</td>
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<td>1.24 (0.92–1.68)</td>
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<tr>
<td>&gt; 0 to &lt; 30</td>
<td>41</td>
<td>1210</td>
<td>1.41 (1.04–2.18)</td>
<td>1.35 (0.93–1.96)</td>
<td>1.35 (0.98–1.85)</td>
</tr>
<tr>
<td>30 to &lt; 60</td>
<td>30</td>
<td>1044</td>
<td>1.94 (1.40–2.66)</td>
<td>1.74 (1.26–2.42)</td>
<td>1.53 (1.15–2.02)</td>
</tr>
<tr>
<td>60 to &lt; 150</td>
<td>39</td>
<td>1082</td>
<td>1.77 (1.35–2.32)</td>
<td>1.45 (1.10–1.90)</td>
<td>1.39 (1.11–1.75)</td>
</tr>
<tr>
<td>≥ 150</td>
<td>57</td>
<td>1785</td>
<td>5.88 (2.80–12.32)</td>
<td>5.36 (2.53–11.36)</td>
<td>4.80 (2.42–9.50)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Risk estimated by odds ratios (and 95% confidence intervals) listed according to cumulative dose with a 2-year lag (Models 1 and 2) and without a 2-year lag (Model 3).

\textsuperscript{b} Adjusted for race/ethnicity, smoker status, and alcohol use. No lag in cumulative dose.

\textsuperscript{c} Adjusted for race/ethnicity, smoker status, and alcohol use. Two-year lag in cumulative dose.

\textsuperscript{d} Adjusted for race/ethnicity, two-year lag in cumulative dose.
smoking and alcohol use. ORs in the highest categories of cumulative dose, 60 g to 149 g and 150 g or more, were very similar to those for 3 or more gabapentin prescriptions for association with cancers of the mouth/pharynx, esophagus, and liver. For vaginal cancer, the OR for a cumulative dose of 60 g to 149 g was lower (but based on only 1 exposed case) and for 150 g or more was higher, but the CIs for both of these cumulative dose levels were wide and clearly encompassed the OR for 3 or more prescriptions. The findings for differences between gabapentin users with and without epilepsy on the basis of cumulative dose (data not shown, available from the authors on request) were similar to those based on number of prescriptions. Notable was this difference for risk of vaginal cancer among those who had received at least 150 g of gabapentin: OR with epilepsy of 11.32 (95% CI = 4.93-25.99); without epilepsy, OR of 0.99 (95% CI = 0.13-7.44).

A change from a 2-year lag to no lag between ascertainment of gabapentin use and the index date had variable but little effect on ORs on the basis of number of prescriptions (Table 3). For cancer of the mouth/pharynx, the OR was somewhat lower for only 1 prescription and somewhat higher for 8 or more prescriptions, the latter becoming statistically significant. For esophageal cancer, the OR was somewhat higher for only 1 prescription and somewhat lower for 8 or more prescriptions, with loss of statistical significance for the former. For liver cancer, ORs for only 1 and for 3 or more prescriptions were somewhat lower and very slightly higher for 8 or more prescriptions. All were somewhat lower for vaginal cancer, the largest reduction for only 1 cancer. Removal of 2-year lag had little effect on the findings for cumulative dose (Table 4). CIs were narrowed for all no-lag analyses because of increased numbers of gabapentin users in all categories.

**DISCUSSION**

Findings with 7.5 additional years of follow-up confirmed only the weak associations for lung cancer and all cancers combined found earlier,1 and none met the stricter criteria1 that we now use for screening drugs for possible carcinogenic effects. Four cancer sites screened positive by our stricter criteria.

We believe that it is important to look carefully at the findings when patients fill only 1 prescription for a drug. They include persons who did not take the drug or took very little of it because of side effects or perceived lack of benefit. Because most prescriptions in our setting are for 100 days or less, we doubt that such short-term use has biological plausibility in causing associations of gabapentin use with these cancers. Even the notability incomplete data regarding alcohol use appeared to indicate confounding by alcohol use, as evidenced by slightly less attenuation of relative risk when this variable was excluded in a sensitivity analysis. Lacking clear evidence for confounding by indication for esophageal cancer, we suggest that associations with cigarette smoking and alcohol might be more important in explaining this cancer’s association with gabapentin use. The ORs for vaginal cancer were also moderately reduced when these variables were added. The most important known risk factors for vaginal cancer appear to be mother’s use of diethylstilbestrol (DES) during pregnancy and human papillomavirus infection.10 We did not have information about these risk factors.

The most striking finding of all the sensitivity analyses was the marked difference in relative risk of vaginal cancer between gabapentin users with and without epilepsy—high risk for the epilepsy subgroup and virtually absent for the nonepilepsy subgroup. This finding was markedly different from this comparison for the other 3 cancer sites, which were mildly in the opposite direction. The difference in risk for vaginal cancer between the 2 indications for gabapentin should be verified in larger numbers of patients. Because epilepsy is not a likely risk factor for vaginal cancer, further study of women with epilepsy in whom vaginal cancer develops may explain our finding.

Other antiepileptic drugs were considered as possible confounders. A variety of evidence suggests that phenobarbital and phenytoin are possibly carcinogenic.11 Varying slightly with cancer site, phenobarbital was received by approximately 10% of users of other antiepileptic drugs and phenytoin by about 18%. Valproate (used by about 16%) has been suggested as possibly preventive because of its antiproliferative effect on cell lines.11 We participated in a collaborative study with outside investigators who hypothesized
Gabapentin and Cancer Risk: Updated Findings from Kaiser Permanente Northern California

prevention of breast cancer in humans by valproate, but a negative association was not confirmed (unpublished written data). In a sensitivity analysis, we controlled for use vs nonuse of antiepileptic drugs other than gabapentin. The increase in ORs went in the direction expected with negative confounding (ie, not contributing to increased risk), and the changes were minimal. The 3 drugs (phenobarbital, phenytoin, and valproate) were each received by a relatively small proportion of other-antiepileptic drug users. Benzodiazepines were by far the most commonly received, accounting for about 45% of the other antiepileptic drugs.

We did not see evidence that socioeconomic status might be an important confounder. When we added as a sensitivity analysis the 2 available indicators of this characteristic to our multivariable analysis, changes in ORs were negligible. Sensitivity analyses based on cumulative dose and on elimination of the 2-year lag did not importantly affect our findings. We have routinely included a 2-year lag in screening pharmaceuticals for possible carcinogenicity because short-term associations have less biological plausibility. Also, a 2-year lag helps to avoid protopathic bias caused by the drug being given for symptoms of cancer before it is diagnosed, thus falsely ascribing a possible carcinogenic effect of gabapentin.

CONCLUSION
In an updated analysis, we find little if any epidemiologic evidence of a carcinogenic effect of gabapentin.

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

Acknowledgments
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How to Cite this Article

References
2. Sigler RE, Gough AW, de la Iglesia FA. Pancreatic acinar cell neoplasia in male Wistar rats following 2 years of gabapentin exposure. Toxicology 1995 Apr 12;98(1-3):73-82. DOI: https://doi.org/10.1016/0300-483x(95)02696-x.

Cancer
… an uneven swelling, rough, unseemly, darkish, painful, and sometimes without ulceration … if operated on, it becomes worse . . . . It has the veins stretched on all sides as the animal the crab (cancer) has its feet, whence it derives.

— Paul of Aegina, 625-690, 7th-century Byzantine Greek physician known as the father of early medical books
Radical Prostatectomy and Pelvic Lymph Node Dissection in Kaiser Permanente Southern California: 15-Year Experience

Pooya Banapour, MD; Andrew Schumacher, MD; Jane C Lin; David S Finley, MD

ABSTRACT

Introduction: Radical prostatectomy (RP) with pelvic lymph node dissection (PLND) is the standard treatment of high-risk prostate cancer. High-risk patients and those with lymph node metastasis (LNM) require further treatment. We review outcomes of RP+PLND in Kaiser Permanente Southern California (KPSC).

Methods: Patients who underwent RP+PLND in KPSC from January 1, 2001, to July 1, 2015 were included. Patient charts were retrospectively reviewed for demographic information and clinicopathologic data which were used to calculate positive surgical margin rate, LNM, adjuvant treatment, 5-year biochemical recurrence, and overall survival. Univariate and multivariate logistic regression analyses were used to identify factors associated with margin positivity.

Results: Patients (N = 1829) underwent RP+PLND (241 high-risk, 943 intermediate-risk, 645 low-risk). Positive margin rates were 17.8%, 14.8%, and 11.9% in the high, intermediate- and low-risk groups. Biochemical recurrence rates were 22% in high-risk and 12.1% in the low-risk category. Androgen deprivation use was 4.1% in the high-risk group and 0.9% in the low-risk group. Five-year overall survival was 92.5% in lymph node-positive patients and 94.9% in lymph node-negative patients (p = 0.8). On multivariate analysis, age (odds ratio [OR] = 1.02, p = 0.02), prebiopsy prostate-specific antigen (OR = 1.02, p < 0.001), and clinical T stage (OR = 1.49, p = 0.01) were associated with margin positivity.

Conclusion: In KPSC, RP+PLND was performed in patients with low-, intermediate-, and high-risk prostate cancer. Age, prebiopsy prostate-specific antigen, and clinical stage were associated with positive surgical margins in patients with LNM. Recipients of RP+PLND with LNM and positive surgical margins required adjuvant treatment.

INTRODUCTION

Prostate cancer affects 1 in 6 men, making it the most common malignancy in men worldwide.1 Because of improvements in screening and detection of prostate cancer in the era of prostate-specific antigen (PSA) testing, various treatment modalities dependent on a patient-physician shared decision-making process have been developed. Regarding more aggressive localized prostate cancer, radical prostatectomy (RP) is becoming the most prevalent treatment modality, primarily because of its lower morbidity rates as well as improved disease-free and overall survival.2-7

As there continue to be more operations performed in patients with higher-risk localized prostate cancer, there has been an increasing number of cases of lymph node metastasis (LNM) discovered after RP. Optimal management of this subset of patients with high-risk prostate cancer is unknown and can be challenging to many urologists. One school of thought involves treatment of such patients with immediate androgen deprivation therapy after RP because it has an improved overall and biochemical recurrence-free survival.6-9 The risks of androgen deprivation, however, encourage many physicians to delay its use until evidence of prostate cancer recurrence has been established. An investigation of the Surveillance, Epidemiology and End Results (SEER) Program database showed that postponing and even omitting androgen deprivation therapy in men with positive lymph nodes after RP does not significantly influence survival.10 Other investigators have shown that positive surgical margins may guide management of these higher-risk patients.11 Although optimal management of lymph node-positive (LNP) patients remains controversial, the patient profile and histopathologic factors such as positive margin rate can help guide therapy. With improvements in biochemical testing, imaging, and advanced therapeutics, the 5-year survival rate in such patients is as high as 85%.12 Nonetheless, results of large multi-institutional studies investigating this population have shown a poorer prognosis relative to their LNM-free cohorts, especially in cases with positive surgical margins.13,14 Daneshmand and colleagues15 have shown that factors such as local tumor burden and percentage of lymph nodes involved with cancer influence disease progression. Other studies have reported a high Gleason score, seminal vesicle invasion, and positive margins as significant negative predictors of disease-free and overall survival in patients with LNM.13-15

To further understand the pathophysiology of LNM, many investigations of risk factors for LNM in such populations have taken place. A retrospective review of the SEER database and the National Cancer Database showed that PSA, clinical stage, and African American race were strong predictors of LNM. Several important models predicting the risk of LNM, the most well known of which was developed by Briganti and colleagues,16 have been used to guide surgical planning and prognostication in high-risk patients. However, these predictive models are limited by their inability to predict the clinical course of patients with LNM, especially in the setting of pathologic positive surgical margins.

The clinical course of patients with positive surgical margins and LNM on pathologic analysis after RP and pelvic lymph node dissection (RP+PLND) can be variable and is poorly understood. Many patients have a modest 10-year disease-free...
survival, whereas others exhibit early biochemical recurrence and progression.\textsuperscript{13-15} Although disease progression and recurrence can depend on the volume of lymph nodes involved, management after prostatectomy of patients with LNM and positive surgical margins remains an unfamiliar territory to many urologists. In this study, we review the Kaiser Permanente Southern California (KPSC) experience with RP+PLND; specifically, we investigate the risk factors, pathologic outcomes, and clinical course of patients with and without LNM to better understand their management.

**METHODS**

**Patient Population**

This retrospective study was approved by the Kaiser Permanente Los Angeles Medical Center institutional review board. Demographic, clinical, and pathologic data were collected retrospectively from the medical charts of patients treated with radical prostatectomy for prostate cancer from January 1, 2001, to July 1, 2015. Patients older than age 18 years with pathologically confirmed prostate adenocarcinoma were included in the study. Surgery was performed at 3 of 9 hospitals in the KPSC Region. Robotic surgeries were included starting in 2008. Standard PLND was performed, including removal of common iliac, external iliac, hypogastric, and obturator lymph nodes. Preoperative data collected included PSA, ultrasound-guided transrectal biopsy pathology, and clinical stage determined by an attending urologist using the most recent American Joint Committee on Cancer staging system. Pathologic assessment was performed of the prostate biopsy specimen and RP specimens, and included the number of cores sampled, the number of positive cores, and stage using the most recent American Joint Committee on Cancer staging system. Follow-up included PSA testing, clinical examination according to the most recent National Comprehensive Cancer Network guidelines, and evaluation of patient charts for assessment of survival.

**Statistical Analysis**

Patients were categorized into low-, intermediate-, and high-risk categories according to their D’Amico risk stratification.

| Table 1. Preoperative clinical and biopsy characteristics of patients with low-, intermediate-, and high-risk prostate cancer |
|-----------------|-----------------|-----------------|
| **Characteristic** | **High risk** (n = 241) | **Intermediate risk** (n = 943) | **Low risk** (n = 645) |
| Age at surgery, y | Mean (SD) | 60.9 (6.55) | 59.6 (7.15) | 58.2 (7.21) |
| | Median | 61.9 | 60.3 | 58 |
| | Q1, Q3 | 56.4, 65.7 | 54.6, 64.8 | 53.3, 64.1 |
| | Range | 42.4-74.9 | 35.5-77.5 | 35.6-77.1 |
| Clinical stage, no. (%) | T1 | 161 (66.8) | 668 (70.8) | 557 (86.4) |
| | T2 | 78 (32.4) | 270 (28.6) | 88 (13.8) |
| | T3 | 2 (0.8) | 5 (0.5) | 0 (0) |
| Prebiopsy PSA, ng/mL | Mean (SD) | 13.3 (13.90) | 11.1 (9.40) | 5.5 (1.94) |
| | Median | 6.9 | 9.2 | 5.3 |
| | Q1, Q3 | 5.2, 22.1 | 5.7, 13.5 | 4.2, 6.7 |
| | Range | (0.5-66.8) | (1.4-121.1) | (0.3-10.0) |
| Biopsy Gleason score | 6, no. (%) | 44 (18.3) | 162 (17.2) | 645 (100) |
| | 7, no. (%) | 0 (0) | 716 (75.9) | 0 (0) |
| | 8, no. (%) | 134 (55.6) | 40 (4.2) | 0 (0) |
| | 9, no. (%) | 62 (25.7) | 22 (2.3) | 0 (0) |
| | 10, no. (%) | 1 (0.4) | 3 (0.3) | 0 (0) |
| Mean (SD) | 7.9 (1.00) | 6.9 (0.58) | 6.0 (0) |
| Median | 8.0 | 7.0 | 6.0 |
| Q1, Q3 | 8.0, 9.0 | 7.0, 7.0 | 6.0, 6.0 |
| Range | 6.0-10.0 | 6.0-10.0 | 6.0-10.0 |
| Preoperative androgen deprivation therapy, no. (%) | No | 209 (86.7) | 880 (93.3) | 639 (99.1) |
| | Yes | 32 (13.3) | 63 (6.7) | 6 (0.9) |

PSA = prostate-specific antigen; Q = quartile; SD = standard deviation.

Mean age, mean prebiopsy PSA, clinical stage distribution, Gleason score distribution, and percentage preoperative hormone use was calculated for each risk category. Positive margin rates, pathologically positive lymph node rates, pathologic stage distribution, recurrence rate, adjuvant hormone therapy use, Gleason score upstaging rate, and Gleason score downstaging rate were calculated for each risk category. Postoperative data, including positive margin rate, clinical stage distribution, recurrence rate, use of adjuvant androgen deprivation therapy, use of adjuvant radiation therapy, Gleason score upstaging rate, Gleason score downstaging rate and survival rate were compared between categories. Recurrence was defined as a biochemical recurrence (2 consecutive PSA values < 0.2 ng/mL) or radiologic evidence of metastasis within 5 years. Adjuvant androgen deprivation therapy was defined as any use of androgen deprivation therapy for prostate cancer after prostatectomy. Patient charts at 5 years after prostatectomy were reviewed, and survival rates were calculated.

Chi-squared analyses were performed to compare categorical variables, and t-tests were conducted to compare continuous variables. Univariate and multivariate models were used to determine factors associated with positive margins. Stata data analysis software (StataCorp LLC, College Station, TX) was used for statistical analysis.

**RESULTS**

A total of 1829 patients underwent radical prostatectomy in KPSC from January 1, 2001, to July 1, 2015. Among the patients, 241 were high risk, 943 were intermediate risk, and 645 were low risk according to D’Amico risk stratification.
total of 783 patients underwent robot-assisted RP (42.8%), 567 patients underwent laparoscopic RP (31%), and 479 patients underwent open RP (26.2%). Preoperative characteristics are displayed in Table 1. The average age at surgery was 60.9 years for high-risk patients, 59.6 years for intermediate-risk patients, and 58.2 years for low-risk patients. Among the high-risk patients, tumors in 161 were cT1 (66.8%), in 78 were cT2 (32.4%), and in 2 were cT3 (0.8%). Of the intermediate-risk patients, 668 had cT1 (70.8%), 270 had cT2 (28.6%), and 5 had cT3 (0.5%) tumors. There were 557 patients with cT1 disease (86.4%) and 88 patients with cT2 disease (13.6%) in the low-risk group. The mean prebiopsy PSA value was 13.3 ng/mL, 11.1 ng/mL, and 5.5 ng/mL in the high-, intermediate-, and low-risk groups, respectively. The mean prebiopsy Gleason score was 8, 7, and 6 in the high-, intermediate-, and low-risk groups, respectively. A total of 13.3% of high-risk patients (n = 32), 6.7% (n = 63) of intermediate-risk patients, and 0.9% (n = 6) of low-risk patients received presurgical androgen deprivation therapy.

Histopathologic data can be seen in Table 2. Positive margin rates were 17.8%, 14.8%, and 11.9% in the high-, intermediate-, and low-risk groups. The rate of pathologic lymph node positivity was 14.9%, 9.8%, and 0.9% in the high-, intermediate-, and low-risk groups. In the high-risk group, 115 patients (47.8%) had pT2 tumors, 125 had pT3 tumors (51.8%) and 1 patient had a pT4 tumor (0.4%). Of the intermediate-risk group, 585 patients (62%) were in the pT2 category, 356 were in the pT3 category (37.7%), and none were in the pT4 category. There were 577 patients with pT2 tumors (89.4%) and 68 with pT3 tumors (10.5%) in the preoperative low-risk group. Gleason score upstaging was highest in low-risk (31.9%) relative to intermediate (17.3%) and high-risk (25.3%) patients. Interestingly, Gleason score downstaging was highest in high-risk (36.1%) relative to low-risk (0%) and intermediate-risk (9.3%) groups.

Table 3 shows 5-year recurrence rates, use of adjuvant androgen deprivation therapy, and adjuvant radiation therapy use in each risk category. The recurrence rate was highest in the high-risk category (22%) and lowest in the low-risk category (12.1%). Adjuvant androgen deprivation use was also highest in the high-risk group (4.1%) and lowest in the low-risk group (0.9%). Patients with intermediate-risk prostate cancer had the highest rate of adjuvant radiation therapy (2.7%) relative to the low-risk (1.9%) and high-risk (2.5%) groups.

Preoperative characteristics for patients with pathologic positive lymph nodes can be seen in Table 4. Of the 1829 patients, 134 (7.3%) were LNP, and 1693 (92.6%) were lymph node negative (LNN). Patients with LNP were not significantly older than patients with LNN (60.7 vs 59.6 years, respectively). There were a larger number of patients with T2 and T3 disease in the LNP group (38.8% and 3.7%, respectively) relative to the LNN group (22.7% and 0.1%, respectively). Median PSA and Gleason score were significantly higher in the LNP group than in the LNN group (PSA, 10.5 ng/μL vs 6.5 ng/μL, p < 0.001; Gleason score, 7.3 vs 6.7, p < 0.001). There was a significantly larger percentage of patients with elevated Gleason scores in the LNP group (Table 4). Further, a larger proportion of LNP patients received preoperative androgen deprivation therapy compared with LNN patients (11.2% vs 5.1%, respectively).

A comparison of postoperative data between LNP and LNN patients is seen in Table 5. The positive margin rate was significantly higher in LNP patients than in LNN patients (23.1% vs 13.5%). Five-year overall survival was 86.9% in patients with positive surgical margins and 92.2% in patients with negative surgical margins. There was an increased prevalence of pathologic T3 disease in LNP patients (88.8% vs 25.4%, p < 0.001). Of note, 1 patient was noted to have T4 disease but did not have lymph node invasion. Gleason score upstaging was higher in LNP patients (35.1% vs 22.6%, p < 0.001). Gleason score downstaging was also higher in LNP patients;
however, this was not statistically significant (p < 0.9). Recurrence rate and adjuvant androgen deprivation therapy use were both higher in LNP patients than in LNN patients (recurrence, 26.1% vs 16.4%, p < 0.05; androgen deprivation, 5.2% vs 1.2%, p = 0.02). Use of adjuvant radiation therapy was not significantly higher in LNN patients (2.5% vs 0.7%, p < 0.9). Compared with LNN patients, LNP patients did not have a significantly lower 5-year overall survival rate (92.5% vs 94.9%, p < 0.9).

Univariate and multivariate analyses were used to identify factors associated with margin positivity in both LNP and LNN groups. Age (odds ratio [OR] = 1.02, p = 0.02), prebiopsy PSA (OR = 1.02, p < 0.001) and clinical T stage (OR = 1.49, p = 0.01) remained significant predictors of margin positivity.

**DISCUSSION**

This study represents the largest retrospective prostatectomy cohort in KPSC. The study summarizes the preoperative and postoperative characteristics of patients who underwent RP+PLND for prostate cancer.

Of the patients who underwent RP, 13% were high risk, 51% were intermediate risk, and 35% were low risk. The percentage in each risk category is consistent with other prostate cancer databases. The average prebiopsy PSA in the high-risk category was 13.3 ng/μL. In a recent study evaluating oncologic outcome in high-risk patients, the prebiopsy PSA was slightly higher at 15.9 ng/μL. This difference may be attributable to aggressive PSA screening and shorter time to surgery caused by in-network care within a managed care system.

In our study, 17.8% of the high-risk, 14.8% of intermediate-risk, and 11.9% of low-risk patients had positive surgical margins after RP. Large RP series have reported a mean positive surgical margin rate ranging from 2% to 31%. The positive surgical margin rates are overall consistent with the literature. The slightly higher positive surgical margin rate for low-risk patients in our series may be because of more aggressive nerve-sparing practices in this subset of patients. Differences in risk stratification between studies may also contribute to differences in positive surgical margin rates. Furthermore, LNP was 14.9% in high-risk, 9.8% in intermediate-risk, and 0.9% in low-risk RP recipients. Large multi-institutional studies have reported LNP ranging from 12.3% to 14% in high-risk patients, consistent with our findings.

Of interest, our study showed a 5-year overall survival of 92.5% in high-risk patients with LNN. Five-year overall survival was 86.9% in patients with positive surgical margins and 92.2% in patients with negative surgical margins. Qin and colleagues showed a cancer-specific survival of 96% in patients with LNM undergoing RP+PLND. Interestingly, all patients in the study received adjuvant androgen deprivation therapy, whereas only 5.2% of high-risk patients with LNM in our cohort underwent adjuvant androgen deprivation therapy. Additionally, 1.2% of patients without LNM received adjuvant androgen deprivation therapy (ADT). Although the influence of adjuvant ADT on survival was not particularly investigated in this study, it is noteworthy that there was no significant difference in 5-year overall survival given the pattern of adjuvant ADT use in patients with intermediate-risk and high-risk prostate cancer. Ideally, prospective randomized long-term studies with standardized criteria for adjuvant ADT would be necessary to investigate its influence on survival. It is clear that in our health care network, adjuvant ADT was administered on a case-by-case basis, taking into consideration margin positivity, LNN, timing and burden of disease recurrence, and patient-specific factors.

### Table 4. Preoperative demographic and clinical characteristics of patients with pathologic positive lymph nodes

<table>
<thead>
<tr>
<th>Lymph node involvement</th>
<th>Lymph node negative (n = 1693)</th>
<th>Lymph node positive (n = 134)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.2 (7.14)</td>
<td>59.9 (7.26)</td>
<td>0.30</td>
</tr>
<tr>
<td>Median</td>
<td>59.6</td>
<td>60.7</td>
<td></td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>54.3, 64.6</td>
<td>54.9, 65.7</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>35.5-77.5</td>
<td>40.8-77.0</td>
<td></td>
</tr>
<tr>
<td>Clinical stage, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>1307 (77.2)</td>
<td>77 (57.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>T2</td>
<td>384 (22.7)</td>
<td>52 (38.8)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>2 (0.1)</td>
<td>5 (3.7)</td>
<td></td>
</tr>
<tr>
<td>Prebiopsy PSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean PSA (SD)</td>
<td>8.9 (8.40)</td>
<td>15.5 (13.17)</td>
<td>0.01</td>
</tr>
<tr>
<td>Median</td>
<td>6.5</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>4.8, 10.2</td>
<td>7.6, 19.2</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>(0.3-121.1)</td>
<td>(2.3-73.0)</td>
<td></td>
</tr>
<tr>
<td>Biopsy Gleason score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.7 (0.81)</td>
<td>7.3 (0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>6.0, 7.0</td>
<td>7.0, 8.0</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>6.0-10.0</td>
<td>6.0-9.0</td>
<td></td>
</tr>
<tr>
<td>6, no. (%)</td>
<td>834 (49.3)</td>
<td>17 (12.7)</td>
<td></td>
</tr>
<tr>
<td>7, no. (%)</td>
<td>641 (37.9)</td>
<td>73 (54.5)</td>
<td></td>
</tr>
<tr>
<td>8, no. (%)</td>
<td>140 (8.7)</td>
<td>28 (19.4)</td>
<td></td>
</tr>
<tr>
<td>9, no. (%)</td>
<td>66 (3.9)</td>
<td>18 (13.4)</td>
<td></td>
</tr>
<tr>
<td>10, no. (%)</td>
<td>4 (0.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Preoperative androgen deprivation therapy, no. (%)</td>
<td>86 (5.1)</td>
<td>15 (11.2)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

PSA = prostate-specific antigen; Q = quartile; SD = standard deviation.
Patients with positive surgical margins in the setting of LNM after RP+PLND require more aggressive follow-up and management. In our cohort, age, prebiopsy PSA and clinical T stage were factors associated with positive surgical margins in patients with LNP disease. Similar factors have been seen in other studies. Although it is well known that patients with LNM and positive surgical margins have a worse prognosis, we investigated the factors influencing biochemical recurrence in this subset of patients. Age, biopsy Gleason score, Gleason score upstaging, and positive margins influenced biochemical recurrence (Table 7). Of note, positive margin status was the most significant factor for biochemical recurrence (OR = 9.23, p < 0.001). Other investigations corroborated positive surgical margins as a strong factor of biochemical recurrence in prostatectomy recipients.

In the KPSC system, RP+PLND has been a standard of care for higher-risk prostate cancer patients. In our 15-year experience, patients with LNM have had more positive surgical margins, higher biochemical recurrence rates, and Gleason score upstaging. Although positive surgical margin was the most significant predictor of biochemical recurrence, it did not significantly influence 5-year survival. Our practice pattern in terms of how to manage patients with LNM and positive surgical margins has not been standardized and occurs on a case-by-case basis with multiple adjuvant treatments, including antiandrogen and radiation therapy.

Our study has several important limitations. First, this was a retrospective cohort study examining all patients who underwent RP for prostate cancer. Although the study is retrospective, the data on high-risk patients with LNM is valuable because randomized controlled trials are limited given the lower contemporary incidence of LNP disease with RP. Although it is limited in its design, the study does include pathologic data and 5-year follow-up with regard to adjuvant treatments and oncologic outcomes. We acknowledge that patient follow-up and data on recurrence rates and survival were limited to 5 years. Longer-term follow-up on overall survival, biochemical recurrence-free survival, and metastasis-free survival would add more value to modifying practice patterns at our institution. Lastly, data on patients who received preoperative or postoperative androgen deprivation therapy and adjuvant radiation therapy was not standardized. Despite this limitation, the influence of postoperative androgen deprivation on survival in high-risk patients with positive lymph nodes in this study remains consistent with the findings of large multi-institutional studies.

**CONCLUSION**

To our knowledge, this study is the largest retrospective prostatectomy cohort summarizing preoperative and postoperative characteristics of patients with prostate cancer undergoing RP+PLND. Positive margin rates were 17.8%, 14.8%, and 11.9% in the high-, intermediate-, and low-risk groups. In multivariate analysis, age, prebiopsy PSA, and clinical stage were predictive of positive margins in patients with LNP disease. Furthermore,
Radical prostatectomy and pelvic lymph node dissection in Kaiser Permanente Southern California: 15-Year Experience


Special Glory

The special glory of the healing arts is self-sufficient and recommends itself to mankind by its value and utility.

— Desiderius Erasmus Roterodamus, 1466-1536, Dutch Christian humanist
This is a story about friendship. Sandhill Crane are fairly social birds that are usually encountered in pairs or family groups through the year. During migration and winter, nonrelated cranes come together to form “survival groups,” which forage and roost together. This picture captured such a group that was calling and waiting for one of their members. I merged and processed 4 original photos to recreate this touching moment.

The pictures were shot at the Bosque del Apache National Wildlife Refuge, New Mexico, US.

Ms Dou worked as a molecular biologist and is an artist living in West Linn, OR. More of her artwork can be seen in other issues of The Permanente Journal.
Feasibility of a Preoperative Anemia Protocol in a Large Integrated Health Care System

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ABSTRACT

Background: Optimizing preoperative anemia is a required component of the Joint Commission Patient Blood Management Certification and an important component of Enhanced Recovery After Surgery.

Objective: To describe a preoperative anemia protocol developed and implemented at the Kaiser Permanente San Jose Medical Center in California to facilitate preoperative identification and treatment of anemia.

Methods: The protocol included all operations at risk of causing substantial blood loss. It excluded emergent operations and those for which the patient had a normal last hemoglobin value within the prior 12 months unless newly developed anemia was suspected. Eligible patients were screened for laboratory evaluation, and those with anemia were treated for reversible causes. Consistency was ensured by physician, staff, and patient education, and by use of electronic health records. Administration of intravenous iron and erythropoietin consultation with specialists were expedited as part of a management algorithm.

Results: Among 510 patients enrolled during 1 year, 442 (87%) received anemia screening laboratory tests. Half of those with laboratory results were eligible for further optimization: 207 had anemia and 21 had iron deficiency without anemia. Among the 228 patients eligible for optimization, 189 (83%) had anemia addressed preoperatively. Of 129 patients with iron deficiency anemia, 102 (79%) received intravenous iron preoperatively, with a mean preoperative increase in hemoglobin level by 0.98 g/dL (n = 79).

Conclusion: Integration of specialty services, optimization of technology, and consistency across practitioners were crucial for successful implementation and sustainability of a preoperative anemia protocol developed to expedite and enhance best practices.

INTRODUCTION

Preoperative anemia is a common yet modifiable condition associated with increased perioperative morbidity, mortality, and blood transfusions.1-3 In the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database of more than 200,000 patients undergoing major noncardiac operations, the incidence of preoperative anemia was 30%.3 Postoperative mortality and morbidity at 30 days were higher in patients with anemia, with consistent differences for varying degrees of anemia. Anemia, when present along with any other known preoperative risk factor, led to a synergistically greater than 10-fold negative effect on outcome.3 The European Surgical Outcomes Study group, in a secondary analysis study of more than 39,000 patients, showed that those with severe or moderate preoperative anemia had significantly longer length of stay and higher rates of inhospital mortality and postoperative admission to the intensive care unit.4

Patient blood management consists of the following 3 pillars: First, identification and treatment of preoperative anemia; second, minimization of surgical blood loss; and third, consideration for the appropriateness of transfusions. Preoperative anemia is associated with poor patient outcomes independent of blood transfusions, and poor outcomes are amplified in transfusion recipients. Prior randomized clinical trials of red blood cell transfusion strategies have demonstrated improved mortality and morbidity with restrictive strategies in medical patients, including patients with upper gastrointestinal (GI) tract bleeding,5,6 and the noninferiority of restrictive strategies in patients with hip fracture and known cardiovascular risk factors.7 Successfully addressing the first pillar with an associated reduction in blood transfusion would support the utility of a preoperative anemia protocol.

Although intravenous (IV) iron has been suggested as a transfusion-sparing strategy in surgical patients,8 it was previously not a part of routine preoperative practice. IV iron infusions, especially the newer-generation formulations, have previously been shown to be safe and efficacious. A recent large systematic review and meta-analysis of all IV iron preparations did not show any increase in severe adverse events or infection rates.9 When high-molecular-weight iron dextran is avoided, IV iron is safe, with an estimated serious adverse event incidence of less than 1:200,000.10 Oral iron often does not improve anemia in preoperative patients because of the high prevalence of functional iron deficiency, poor compliance owing to its common GI side effects, and poor absorption caused by inflammatory bowel disease, celiac disease, Helicobacter pylori infection, history of gastric bypass or small-bowel resections, or concomitant use of antacids or proton pump inhibitors. Even in cases of good oral iron absorption, oral repletion generally takes 3 to 6 months,8 a lengthy time frame often not feasible in the preoperative patient. Additionally, oral iron replacement may not be adequate for those with ongoing bleeding issues before the operation.8

Although evidence points to a need for comprehensive preoperative anemia programs, few such programs exist in the US. Efficient methods for early identification and timely treatment of preoperative anemia are lacking. Many patients with...
anemia proceed directly to an operation with minimal to no optimization.1 Mild anemia, especially when chronic, is often not recognized because of a tendency to normalize these frequently seen but abnormal laboratory findings. Moderate to severe anemia is also frequently not addressed preoperatively because of the lack of lead time between identification and the operation date, resulting in few options for optimization other than last-minute surgery cancellation. To address these gaps, we have developed and implemented a preoperative anemia protocol to enhance the early recognition and timely treatment of anemia.

METHODS

Setting

Kaiser Permanente (KP) is a large integrated health care delivery system in the US with a physician-led corporation, health insurance partner, and hospitals and clinics for coordinating inpatient and outpatient care. The KP San Jose Medical Center in California has 242 licensed hospital beds. In 2016, a total of 6683 Ambulatory Surgery Unit and 5048 hospital operating room cases, including a large variety of general and specialty operations, were performed. The KP San Jose site is a regional referral center for spine, colorectal, hepatobiliary, and hand reconstructive operations but does not perform bariatric or cardiothoracic operations. At the time of this study, KP San Jose’s Perioperative Medicine Clinic staffing included 3 full-time equivalent (FTE) physicians, 1 FTE nurse practitioner, 1.2 FTE registered nurses, 1.8 FTE medical assistants, and 1 FTE clerk for reception and schedule maintenance.

Study Cohort

The study included all adults (≥ 18 years of age) eligible for the preoperative anemia protocol in a 1-year period between June 1, 2016 and May 31, 2017 who underwent evaluation at the KP San Jose Perioperative Medicine Clinic. The protocol was first instituted on January 25, 2016 with numerous initial adjustments and standardizations made on the basis of clinical experience. An initial washout implementation period was intentionally excluded from data analysis.

Preoperative Anemia Protocol

In 2015, KP San Jose established a Preoperative Anemia Steering Committee with the objective to design and implement a protocol that would enhance the early recognition and timely treatment of anemia. Through an iterative process with input from the Surgery, Anesthesiology, Perioperative Medicine, Nephrology, Gastroenterology, and Hematology Departments, a protocol was developed to identify patients with anemia preoperatively and to recommend a progression of evidence-based interventions.

Inclusion and Exclusion Criteria

Included were all operations at risk of causing substantial blood loss at KP San Jose—defined as hysterectomies, all bowel operations excluding appendectomy, all solid organ resections excluding prostate, and included Whipple procedures, mastectomies only if accompanied by reconstruction, all hip and knee arthroplasties, all multilevel spine operations, and all major vascular surgeries including carotid, femoral popliteal bypass, and abdominal aortic aneurysm (open or endovascular) procedures. Exclusion criteria were age younger than 18 years, emergent operations (within 48 hours of case request and operation during current hospitalization), and patients with a last hemoglobin value within normal limits in the past 12 months before surgical case creation.

Protocol Case Identification

A daily, encrypted patient spreadsheet report was developed to extract surgical cases created the previous day, which were then filtered by inclusion and exclusion criteria to capture major operations at risk of causing substantial blood loss and patients who were more likely to have anemia. Filterable fields included patient’s sex and last hemoglobin value as well as operation type, location, and date (Figure 1). Electronic identification of patients was conducted each business day by a perioperative medicine nurse, and subsequent manual identification of patients was conducted by a perioperative medicine physician during routine preoperative evaluations. Manual identification included cases missed by screening because of an evaluation by the perioperative medicine physician scheduled on the day of case creation, cases missed on the spreadsheet because of case request from surgeons at a separate KP facility, and cases enrolled per physician discretion (eg, if a recent bleeding history warranted a suspicion of anemia development despite the last known hemoglobin level within 1 year to be within normal limits).

Figure 1. Enrollment, spreadsheet report, and filters.

AAA = abdominal aortic aneurysm; fem pop = femoral popliteal; MD = physician; POM RN = perioperative medicine registered nurse.
Feasibility of a Preoperative Anemia Protocol in a Large Integrated Health Care System

**Protocol Interventions**

At the time that the preoperative anemia protocol went live on January 25, 2016, all KP San Jose perioperative medicine physicians, nurses, and staff were trained regarding implementation. Committee members held periodic meetings to discuss any protocol issues and revisions. Ongoing continuing medical education and electronic health record (EHR) training sessions were held to improve physician education and adherence to the protocol.

Protocol definitions of anemia and iron deficiency, and recommendations for IV iron therapy, were adopted from previously published guidelines. The World Health Organization definition of anemia for men is hemoglobin level below 13 g/dL and for women is hemoglobin level below 12 g/dL. A trial of IV iron intervention is recommended when a hemoglobin level of 12 g/dL and for men and hemoglobin level of 11 g/dL for women, in addition to in a ferritin level below 22 mg/L or transferrin saturation below 14% using KP San Jose laboratory references of lower than normal range.

Patients with abnormal laboratory findings according to the anemia protocol were scheduled for an anemia evaluation with a perioperative medicine physician. These anemia-focused appointments were generally held up to 30-minute telephone evaluations done before and in addition to the patient’s usual preoperative evaluations. Spreadsheet filters and electronic patient lists were developed to enroll and track patients. EHR tools, including order preference lists and electronic note templates with built-in decision guidance, were developed to document and guide anemia management to ensure consistency and completeness. Creation of standing orders for staff helped with physician workload. An IV iron table was created using the Ganzoni formula to simplify iron replacement calculations (Figure 2).

The IV iron infusions took place in our infusion center. Perioperative medicine physicians ordered ferric carboxymaltose and electronically routed the patient’s chart to the infusion center. A checklist was completed to schedule and administer IV iron within 2 business days of request, which included algorithms to identify and optimize iron replacement or those with a hemoglobin level below 11 g/dL undergoing joint replacement or those with a hemoglobin level below 10 g/dL undergoing multilevel spine procedures. A pharmacy-led erythropoietin and IV iron sucrose program for treatment of anemia of renal disease was condensed to 6 weeks. Gastroenterology consultants were committed to providing expedited evaluations, including endoscopy if needed, within 1 week of referral for suspected GI tract blood loss.

**Statistical Analysis**

Continuous variables were reported as means for normally distributed variables and as median values for nonnormally distributed variables. These data were analyzed using the Student t-test, analysis of variance, or the Kruskal-Wallis equality-of-populations rank test as appropriate. Categorical variables were reported as percentages and analyzed using the χ² or Fisher exact tests. All analyses were performed using SAS Version 9.3 (SAS Institute, Cary, NC).

Approval for the study was obtained from institutional review boards of KP Northern California (KPNC). A waiver of informed consent was obtained because this cohort study was retrospective.

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**Figure 2. Intravenous (IV) iron table to calculate dose of ferric carboxymaltose on the basis of body weight (Wt) and starting hemoglobin (Hgb).**

<table>
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<tr>
<th>Wt</th>
<th>50</th>
<th>55</th>
<th>60</th>
<th>65</th>
<th>70</th>
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<th>80</th>
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<tr>
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<td>Dose</td>
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<td>697</td>
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<td>464</td>
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<td>536</td>
<td>572</td>
<td>607</td>
<td>643</td>
<td>679</td>
</tr>
</tbody>
</table>

Note: Black shading indicates 2 doses of 750 mg of IV ferric carboxymaltose administered at 1 week apart. White shading indicates 1 dose of 750 mg of IV ferric carboxymaltose. Hemoglobin (Hgb) concentration to be corrected to 14 g/dL. Iron to replenish stores = 5 mg/kg. Iron deficit (mg) = body weight (kg) x (14 - Hgb) x (2.145) + iron to replenish stores (mg).
Figure 3. Swim-lane diagram of preoperative anemia screen workflow.

B12 = vitamin B12; CBC = complete blood cell count; Cr/GFR = creatinine/glomerular filtration rate; Hg = hemoglobin (g/dL); lab = laboratory; labs = laboratory blood samples; MD = physician; N = no, POM MD = perioperative medicine physician; POM RN = perioperative medicine nurse; RN = registered nurse; TIBC/Fe = total iron-binding capacity/iron; Y = Yes.

Figure 4. Swim-lane diagram of anemia workflow—surgery cannot be delayed.

CBC = complete blood cell count; EPO = erythropoietin; GFR = glomerular filtration rate; Hg = hemoglobin (g/dL); IV = intravenous; PCP = primary care physician; POM MD = perioperative medicine physician; TSAT = transferrin saturation.
Feasibility of a Preoperative Anemia Protocol in a Large Integrated Health Care System

RESULTS

The incidence of preoperative anemia was 20% for all operations and 22% for those who were admitted to the hospital postoperatively according to KP San Jose 2014 data. The admitted group was older, had more complex medical issues, and underwent more complex operations.

A cohort of 510 operations during 1 year, from June 1, 2016 to May 31, 2017, was enrolled in the preoperative anemia protocol. For patients with multiple qualifying operations, only the first operation was counted to avoid confounding postoperative anemia.

Baseline characteristics of the cohort showed a mean age of 60.2 years, median operating room time of 1.83 hours, 56.00% women, and racial distribution of 52.00% white, 5.60% African American, 22.55% Hispanic, 14.31% Asian/Pacific Islander, and 4.90% other races. American Society of Anesthesiologists classes 2 and 3 occurred in 67.45% and 27.25% of the cohort, respectively. Operations included 168 multilevel spinal operations (32.94%), 106 total knee arthroplasties (20.78%), 66 total hip arthroplasties (12.94%), 77 hysterectomies (15.10%), 24 mastectomies with reconstruction (4.71%), 8 Whipple procedures.

Figure 5. Swim-lane diagram of anemia workflow—surgery can be delayed (elective). CBC = complete blood cell count; EPO = erythropoietin; GFR = glomerular filtration rate; GI = gastroenterologist; Hg = hemoglobin (g/dL); IV = intravenous; lab = laboratory test; labs = laboratory blood samples; MD = physician; N = no; pConsult = curbside or telephone consultations; POM = perioperative medicine; retic = reticulocyte count; RN = registered nurse; TSAT = transferrin saturation (%); Y = yes.

Figure 6. Results on feasibility of preoperative anemia protocol.

246 (Hg abnormal) + 264 (no Hg) with eligible surgeries = 510 total eligible for enrollment on the basis of criteria from 6/1/16-5/31/17 (1-year duration)

442 (87%) completed anemia screening labs (at a minimum including Hg, ferritin, and TSAT)

21 iron deficiency without anemia (Ferritin < 22 or TSAT < 14 by KP lab reference range in the absence of anemia, Hg ≥ 12 in women or ≥ 13 in men)

207 abnormal Hg of < 12 in women or < 13 in men

228 eligible for further optimization

189 (83%) had anemia addressed in a POM note

Hg = hemoglobin (g/dL); KP = Kaiser Permanente; lab = laboratory test; labs = laboratory blood samples; POM = Perioperative Medicine Clinic; TSAT = transferrin saturation (%).
Feasibility of a Preoperative Anemia Protocol in a Large Integrated Health Care System

Anemia screening laboratory blood draw occurred at a median time of 28.5 days before the operation (Table 1). Most of the cohort, 442 patients (87%), received anemia screening laboratory tests, with half of those meeting criteria for further optimization (Figure 6). Patients counted as missing screening laboratory tests included those who had anemia-related laboratory tests outside KP such as in skilled nursing facilities, those who missed electronic and manual enrollment, and those who were enrolled but did not follow through to obtain laboratory tests or had cancellation of their operation. Non-KP laboratory results could not be extracted but were seen on chart reviews to investigate those with missing laboratory test results.

Those with normal laboratory findings were early graduators of the protocol. The remaining 228 patients were eligible for optimization, including 207 who were anemic and 21 who were iron deficient without anemia; 83% of those eligible had anemia addressed preoperatively. Of 129 patients with either classic or functional iron deficiency anemia (transferrin saturation < 20% or ferritin level < 100 ng/mL), 102 (79%) received IV iron with either ferric carboxymaltose or iron sucrose; 5 nephrectomies (0.98%), 3 abdominal aortic aneurysm repairs (0.59%), and 53 other operations (10.39%).

**Table 1. Baseline characteristics of study cohort**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>60.6 (13.4)</td>
</tr>
<tr>
<td>Duration of surgery, hrs, median (IQR)</td>
<td>1.83 (1.53)</td>
</tr>
<tr>
<td>Women</td>
<td>285 (55.88)</td>
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<tr>
<td>Men</td>
<td>225 (44.12)</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>29 (5.7)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>267 (52.35)</td>
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<tr>
<td>African American</td>
<td>30 (5.88)</td>
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<tr>
<td>Hispanic non-black</td>
<td>115 (22.55)</td>
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<tr>
<td>Asian/Pacific Islander</td>
<td>73 (14.31)</td>
</tr>
<tr>
<td>Native American/multiracial/other/unknown</td>
<td>25 (4.90)</td>
</tr>
<tr>
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<tr>
<td>1</td>
<td>23 (4.51)</td>
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<tr>
<td>2</td>
<td>344 (67.45)</td>
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<tr>
<td>3</td>
<td>139 (27.25)</td>
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<tr>
<td>4</td>
<td>4 (0.78)</td>
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<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>168 (32.94)</td>
</tr>
<tr>
<td>Knee replacement</td>
<td>106 (20.78)</td>
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<tr>
<td>Hysterectomy</td>
<td>77 (15.10)</td>
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<tr>
<td>Hip replacement</td>
<td>66 (12.94)</td>
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<tr>
<td>Mastectomy with reconstruction</td>
<td>24 (4.71)</td>
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<tr>
<td>Whipple procedure</td>
<td>8 (1.57)</td>
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<tr>
<td>Nephrectomy</td>
<td>5 (0.98)</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>3 (0.59)</td>
</tr>
<tr>
<td>Other</td>
<td>53 (10.39)</td>
</tr>
<tr>
<td>Days from anemia screening lab collection date to surgery, median (IQR)</td>
<td>28.5 (32.5)</td>
</tr>
</tbody>
</table>

* Data are No. (%) unless indicated otherwise.

ASA = American Society of Anesthesiologists; BMI = body mass index; IQR = interquartile range; SD = standard deviation.

B₁₂ = vitamin B₁₂; GFR = glomerular filtration rate; GI = gastroenterology; Hg = hemoglobin (g/dL); IV = intravenous; POM MD = perioperative medicine physician; preop = preoperatively; TSAT = transferrin saturation (%).
and 7 gastroenterology consults were requested by perioperative medicine physicians (Figure 7). Because other physicians, including primary care physicians and surgeons, also requested for select gastroenterology consults, 19 patients had GI tract endoscopy completed within 6 months before the operation date. Iron deficiency without anemia, identified in 21 patients, was treated via physician discretion, receiving either or both IV iron infusion and oral iron supplementation. These iron deficiency without anemia cases were identified in patients who had no baseline hemoglobin level in the last 12 months before case creation or who were manually included in the protocol via physician discretion. Seven vitamin B₁₂ deficiencies were identified in the entire cohort, of which 4 had vitamin B₁₂ deficiency without anemia and 3 had vitamin B₁₂ deficiency with anemia. All vitamin B₁₂ deficiencies were addressed by supplementation and routing follow-up request to primary care. A total of 75 patients had anemia of other causes, including chronic kidney disease and kidney disease.

In the data analysis of 79 patients, who had received IV iron preoperatively and had hemoglobin levels measured after iron infusion but before surgical incision, the mean change in hemoglobin level was an increase of 0.98 g/dL. Most patients (72%) responded with a hemoglobin increase. A linear relationship was observed between time and delta (Δ, change in) hemoglobin, such that longer times led to a greater increase in hemoglobin (Figure 8).

**DISCUSSION**

The Joint Commission has recognized the importance of treating preoperative anemia, a required component since 2016 for hospitals seeking its Certification in Patient Blood Management. Addressing preoperative anemia is also a key component of Enhanced Recovery After Surgery (ERAS) protocols. A few preoperative anemia clinics have been created at US medical centers in recent years, including the Duke Perioperative Enhancement Team program for orthopedic operations. Our protocol was not limited to orthopedic or elective operations, although orthopedic operations accounted for 67% of our cohort (33% multilevel spine operations, 21% total knee arthroplasties, and 13% total hip arthroplasties). We believe these results can be extrapolated to nonorthopedic operations because preexisting medical conditions are not different enough to alter the management of preoperative anemia.

In 2014, KP San Jose’s incidence of preoperative anemia was lower than those in previously published reports possibly because of integrated health services in our patient population and increased recognition of anemia in recent years; our incidence of anemia as defined by World Health Organization criteria of hemoglobin less than 12 g/dL in women and less than 13 g/dL in men, was 22% among surgeries with at least 1 overnight stay vs 36% in a large series of patients undergoing major surgical procedures (N = 3342; 44.5% women, anemia defined as Hg < 13 g/dL in both sexes) between 2008–2014 and vs 30% in NSQIP data on patients undergoing major noncardiac surgical procedures in 2008 (N= 227,425; 57.6% women, anemia defined by World Health Organization criteria). Patients undergoing nonemergent operations were routinely evaluated by our Perioperative Medicine Clinic, providing a unique opportunity for us to implement the protocol. We developed algorithmic strategies to treat and optimize anemia, and these can be disseminated on a large scale to potentially benefit many patients. Without exposing patients to substantial risk or harm, this protocol enhances and expedites best practices, including IV iron therapy, erythropoietin injections, and gastroenterology and nephrology consultations to meet the timeline requirements of the surgery date. No severe adverse reactions occurred in this cohort as a result of any protocol interventions. There were no delays to operation caused by any side effects from IV iron treatment.

Integrated EHR and patient care across all specialties were crucial to the successful implementation of the protocol. Development of encrypted patient spreadsheet reports, electronic templates with built-in decision guidance, and other EHR tools helped with enrollment, tracking, and workload. KP San Jose was well positioned to garner institutional support and achieve the participation and collaboration of various internal departments, including Perioperative Medicine, Surgery, Nephrology, Gastroenterology, Hematology, and the Infusion Clinic. Although individual protocol interventions are often recommended care for anemic nonsurgical patients, they were standardized and executed with the prevention of surgery delays in mind. Inclusion and exclusion criteria were designed to capture major operations at risk of causing substantial blood loss and patients who were most likely to have preoperative anemia. The protocol captured most patients who would likely
benefit; 442 (87%) of the eligible cohort obtained anemia screening laboratory tests, and approximately half of these had abnormal laboratory results, which led to sequential considerations and interventions. Most patients with iron deficiency anemia (n = 102, 79%) received IV iron therapy, and those indicated received gastroenterology consultations and endoscopic evaluations. Iron deficiency anemia is a low-hanging fruit in terms of its prevalence and amenability to preoperative optimization, and we successfully targeted its identification and optimization among a heterogeneous cohort. Most patients responded to IV iron with an increase in hemoglobin levels. In our cohort, the most prevalent causes of anemia were classic and functional iron deficiencies, together accounting for 62.31% of anemia. Some IV iron deficiency cases likely also had concomitant anemia of chronic disease. Iron deficiency without anemia was also identified as expected, given that iron deficiency is known to precede the development of anemia, and its importance may be magnified in anticipation of substantial surgical blood loss. This subgroup was treated at the discretion of perioperative medicine physicians with either IV or oral iron supplementation and an as-needed bowel regimen.

In addition to expediting and enhancing best practices, the Preoperative Anemia Protocol has improved the early identification and management of cancer, GI tract bleeding, liver disease, and vitamin B₁₂ and iron deficiencies. The early detection of colon cancer has been lifesaving. A woman scheduled for total knee arthroplasty was newly identified to have iron deficiency anemia via protocol screening laboratory test results. After expedition of gastroenterologic procedures within 1 week as a part of the protocol, colonoscopy revealed a cecal mass; her elective knee arthroplasty was postponed, and IV iron therapy and right hemicolectomy were expedited. Surgical pathologic findings showed adenocarcinoma, fortunately with clean margins. She eventually completed elective knee arthroplasty without complications, but this alteration in sequence of management likely avoided unnecessary metastasis, thromboembolic risk, and malignancy-related bleeding risk during postoperative deep venous thrombosis prophylaxis.

We would like to point out several limitations of the study. Because our Perioperative Medicine Clinic consisted of 14 rotating hospitalists who make up a total of 3 FTE physicians, we expected a number of protocol violations because of the need for more education, new physician onboarding, and variance in practice styles. A number of violations were caused by patient noncompliance with laboratory blood draws or IV iron infusions, delays in infusion scheduling where surgery delay was not warranted because the minimum hemoglobin target of either 10 g/dL or 11 g/dL was already met, and physician discretion in which oral instead of IV iron supplementation was prescribed. A few missed identifications, interventions, or follow-up laboratory tests occurred because of missed tracking, because a combination of electronic and manual tracking methods were used. Physicians were manually ordering follow-up laboratory tests for the day of surgery, and some orders were missed or done before the day of surgery; those missing Δ hemoglobin were not included in the analysis shown in Figure 8. Overall, protocol violations were low, demonstrating the feasibility and sustainability of the protocol. Greater hemoglobin response would be anticipated with earlier IV iron administration because a linear relationship was observed between time and increase in hemoglobin before operation. IV iron is expected to increase hemoglobin by 2 g/dL in a 3-week period. Among the 79 patients with hemoglobin tracking any time before surgery, including the day of surgery, 34 patients (43%) of recipients had fewer than 14 days between iron infusion and day of operation, which resulted in a mean increase in hemoglobin level of 0.98 g/dL. Although suboptimal lead time for IV iron therapy limited the preoperative hemoglobin response, iron replacement is still expected to benefit patients in the postoperative period.

IV iron was a key intervention in our protocol given its better correction of functional iron deficiency and faster repitition of iron stores compared with oral iron. We chose ferric carboxymaltose because a 750-mg dose can be conveniently infused during 15 minutes at 1 to 2 doses preoperatively to replete the entire iron deficit for most patients. This choice has been reported to lower the cumulative risk of infusion reactions and extravasations, and to reduce appointments and staff utilization.

Ferric carboxymaltose is approved by the US Food and Drug Administration for the treatment of iron deficiency anemia in adults with intolerance or unsatisfactory response to oral iron and for the treatment of iron deficiency anemia in adults with nondialysis-dependent chronic kidney disease. Bypassing an oral iron trial, as we did, has been previously proposed in the literature. Our acquisition cost of IV iron was similar to packed red blood cell (PRBC) transfusions during the study period at $1.03 per milligram of ferric carboxymaltose vs $244 per unit of PRBCs (containing 250 mg of elemental iron at $0.97 per milligram of iron). However, IV iron infusion is more cost-effective because it requires less patient and staff time compared with PRBC infusions. IV iron infusion can replace the entire iron deficit preoperatively, whereas PRBCs are not indicated for transfusion to a normal hemoglobin level because blood transfusion is known to increase perioperative morbidity and mortality and to carry substantial risks.

Since this cohort, efforts have been ongoing to reduce variability, expedite iron administration, and increase upstream identification. KP San Jose has transitioned to a pharmacist for the ordering of IV iron, vitamin B₁₂, and folic acid supplementations, erythropoietin injections, and follow-up laboratory studies. We have shifted to the use of low-molecular-weight iron dextran, which costs about one-fourth of ferric carboxymaltose and can be infused in 2 hours as a 25-mg test dose followed by 975 mg with similar safety, efficacy, and convenience. A modified version of this protocol is being...
evaluated for scale-up across 21 KPNC hospitals. The patient spreadsheet report initially developed at KP San Jose has been adopted regionally to help with various perioperative optimization projects. Once implemented to all KPNC hospitals serving more than 4.1 million members, and ultimately to KP across the US serving more than 11.8 million members, the KP Anemia Protocol is expected to become the largest such protocol in the US.

CONCLUSION

We believe that perioperative outcomes, including the incidence of perioperative blood transfusions, will be improved by correcting hemoglobin levels preoperatively. Existing literature shows the increase in morbidity and mortality associated with perioperative anemia and indicates the need for IV iron infusion and other anemia-correcting interventions preoperatively. Outcomes data are still lacking from a preoperative anemia protocol to show increased preoperative hemoglobin levels, reduced perioperative blood transfusions, reduced length of stay, and reduced perioperative mortality and morbidity. A recent Australian study randomly assigned 72 patients with iron deficiency anemia to IV iron vs usual care.21 The IV iron group had a reduction in blood transfusions and an association with shorter hospital stay, but was limited by early termination, according to its authors. The PREVENTT trial is a currently ongoing randomized controlled trial in the UK examining clinical outcomes in the use of ferric carboxymaltose for perioperative anemia before major open abdominal operations.22 We plan to measure the important perioperative outcomes of our protocol compared with historical controls for a future publication. 

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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How to Cite This Article


References

ABSTRACT

Introduction: Rapid adoption of robotics has introduced a paradigm change in prostate cancer treatment, with more than 80% of prostatectomies performed robotically in 2015. For treatment of renal cell carcinoma (RCC), this change has not previously been reported. We evaluated trends in surgical management of RCC in Kaiser Permanente Southern California (KPSC) within the last 16 years, especially after adoption of robotics.

Methods: From January 1999 to September 2015, all KPSC members who underwent surgical treatment of suspected RCC were included retrospectively. Surgical approach, patient age, sex, clinicopathology, Charlson Comorbidity Index, and chronic kidney disease status were analyzed using robust Poisson multivariate regression.

Results: The study included 5237 patients. Partial nephrectomy was increasingly used during the study period, and its use surpassed radical nephrectomy in 2012. In a multivariate model, partial nephrectomy was associated with lower pathologic tumor stage (p < 0.001) and lower Charlson Comorbidity Index (p = 0.004) vs radical nephrectomy. Robot-assisted laparoscopic partial nephrectomy (RALPN) started in KPSC in March 2011, and its relative use among all RCC surgeries increased in the following 3 years by 125%, 45%, and 14%. Laparoscopic partial nephrectomy and laparoscopic radical nephrectomy were the most frequently used surgical approaches for localized RCC when RALPN started in 2011. However, RALPN surpassed laparoscopic partial nephrectomy and laparoscopic radical nephrectomy in 2012 and 2014, respectively.

Conclusion: During our study, partial nephrectomy became the most common surgery for treatment of localized RCC. Since 2014, RALPN has become the most common renal oncologic surgical modality in KPSC.

INTRODUCTION

Renal cell carcinoma (RCC) is among the 10 most common cancers in both men and women (> 60,000 new cases per year, lifetime risk approximately 1.6%), with RCC comprising approximately 9 of 10 kidney cancers.\(^1\) Although radical nephrectomy was the standard of care in the past, the increased use of partial nephrectomy (PN) has correlated with the increased incidence of T1 renal masses owing to earlier detection.\(^2,3\) Current management options for patients with renal masses include surgery (radical nephrectomy or PN), ablative therapy (cryoablation and radiofrequency ablation), and active surveillance. The American Urological Association Practice Guidelines released in November 2009 recommended consideration of PN as a standard of treatment of small renal masses.\(^4\) The 2017 guidelines on localized RCC suggested that urologists should prioritize PN as the preferred surgical treatment of clinical T1a renal masses (< 4 cm) to minimize the risk of chronic kidney disease.\(^5\) Rates of active surveillance, as well as minimally invasive ablative techniques, have also increased, particularly in the elderly population.\(^6\) Extensive studies highlighting the use of each surgical modality in the 21st century have shown PN to have equivalent oncologic outcomes to radical nephrectomy, even for patients with larger T2 tumors, with the advantage of preserving nephrons and maximizing postoperative renal function.\(^7,8\) Furthermore, PN is being performed in patients with complex tumors, particularly at academic and high-volume centers.\(^9\)

The emergence of robotics in urologic surgery has resulted in a paradigm shift in prostate cancer management, with more than 80% of all prostatectomies for prostate cancer being performed robotically in recent years.\(^10\) To our knowledge, this trend has not been described for RCC. Robot-assisted laparoscopic partial nephrectomy (RALPN) has been shown to have oncologic and functional outcomes similar to open partial nephrectomy (OPN), with improved perioperative outcomes and significantly fewer perioperative complications compared with a laparoscopic approach, even in those with complex renal tumors.\(^11,12\) We hereby include 16 years of trends in surgical management of RCC, with particular attention to the changes after introduction of robotics in our integrated health care system, Kaiser Permanente Southern California (KPSC).

METHODS

Consisting of 14 Medical Centers and hundreds of adjacent outpatient offices serving more than 4.2 million patients, KPSC has a racial and socioeconomic diversity reflective of the population of Southern California.

We performed an institutional review board–approved multicenter retrospective review of patients who underwent treatment of suspected RCC in our health care system from January 1999 to September 2015. The following treatment modalities were included in the final analysis: Open radical nephrectomy (ORN) and laparoscopic radical nephrectomy (LRN), OPN, laparoscopic partial nephrectomy (LPN), RALPN, and thermal ablation.

Four KPSC Medical Centers have a Da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA), and a core group of 22 robotic surgeons had experience with at least 100 robotic cases before receiving robotic privileges. This group of surgeons
also serves as the privileging body for all approved robotic procedures for KPSC. In March 2011 RALPN was approved in KPSC. All patients age 18 years or older who underwent treatment of suspected localized RCC were included in our study. They were identified using the cancer registry as well as our electronic medical records. International Classification of Diseases, Ninth Revision and Current Procedural Terminology codes were used to extract patient clinicopathologic data as well as treatment modality. This included patient age, race, sex, Charlson Comorbidity Index (CCI), preoperative chronic kidney disease Stage 3 or later (defined as estimated glomerular filtration rate < 60 mL/min/1.73 m², calculated using the modification of diet in renal disease equation¹), hypertension, diabetes, tumor size as defined by pathologic T stage, and the year surgery was performed. Patients with locoregionally advanced disease, those who underwent multivisceral resection, as well as those who underwent renal surgery for nononcologic indications, were excluded from the analysis. Table 1 shows all exclusionary criteria.

We plotted descriptive trends of PN, radical nephrectomy, and ablations as a percentage of total surgeries for the entire study period. Additionally, we plotted trends for RALPN vs other treatment modalities beginning in 2008, when more details about specific treatment modalities beyond simply PN or radical nephrectomy became available in our electronic medical databases. We investigated factors associated with the use of PN vs radical nephrectomy from 2009 (the year of release of the new American Urological Association guidelines on management of small renal masses) to 2015 using χ² and analysis of variance statistical tests as well as multivariate analysis. A separate subanalysis using similar methods was performed looking at PN performed from 2011 to 2015, after RALPN was approved in our system, to examine factors associated with minimally invasive (RALPN or LPN) vs open approach. Of note, radical nephrectomy is not approved as a routine procedure on the robotic platform. Multivariate analyses used robust Poisson regression, which included quadratic time trends and

<table>
<thead>
<tr>
<th>Table 1. Exclusionary criteria</th>
<th>No. excluded</th>
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</thead>
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<tr>
<td>Ureteral tumor</td>
<td>150</td>
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<tr>
<td>Nephroureterectomy</td>
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<tr>
<td>Splenectomy</td>
<td>4</td>
</tr>
<tr>
<td>Hepatic resection</td>
<td>14</td>
</tr>
<tr>
<td>Pancreatic resection</td>
<td>21</td>
</tr>
<tr>
<td>Bowel or colon resection</td>
<td>92</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>96</td>
</tr>
<tr>
<td>Donor nephrectomy</td>
<td>1</td>
</tr>
<tr>
<td>Acute or chronic pyelonephritis</td>
<td>66</td>
</tr>
<tr>
<td>Renal or perinephric abscess</td>
<td>40</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>49</td>
</tr>
<tr>
<td>Renal laceration or disruption of renal parenchyma</td>
<td>3</td>
</tr>
</tbody>
</table>

Figure 1. Patient cohort sizes

AUA = American Urological Association; LPN = laparoscopic partial nephrectomy; OPN = open partial nephrectomy; PN = partial nephrectomy; RALPN = robot-assisted laparoscopic partial nephrectomy; RN = radical nephrectomy.
included all covariates previously mentioned. All p values were based on 2-sided tests of significance, with statistical significance set at p < 0.05.

**RESULTS**

A total of 717 patients were excluded from our study because of potential confounding diagnoses or concomitant surgery (Table 1). The flowsheet in Figure 1 explains how the size of each cohort was determined. The total number of radical nephrectomy, PN, and ablative procedures performed in the remaining 5237 patients are depicted in Figure 2, which highlights the increased use of nephron-sparing surgery from 1999 through 2014. PN was increasingly performed during the study period; the percentage of all RCC patients undergoing PN increased yearly from 2009 to 2013. Given that data were not collected for the full calendar year of 2015, that last year of the study period was omitted from Figure 2. Because of medical and procedural coding changes in 2008, we were unable to accurately assess the surgical approach (laparoscopic vs open) for a large portion of PNs (60.5%, 290 of 479) and radical nephrectomies (61.4%, 979 of 1592) performed from 1999 to 2007. Thus, the graphic presentation of specific surgical approach focuses on 3163 patients treated from 2008 to 2015.

The percentage of each surgical approach as a total of all treatment modalities per year is shown in Figure 3. In March 2011, RALPN was approved by our robotics committee, and in the following 3 years its use increased per year by 125% (2012), 45% (2013), and 14% (2014). When RALPN was approved in 2011, LPN and LRN were the most frequently used surgical approaches for localized RCC. However, RALPN surpassed LPN and LRN in 2012 and 2014, respectively. Nephron-sparing surgery was increasingly performed throughout the study period, with PN accounting for 33.6% of surgeries in 2007 to 2009, compared with 48.6% of surgeries in 2010 to 2013 (p < 0.001).

We performed a subanalysis comparing factors associated with the use of PN and radical nephrectomy from 2009 to 2015. Neither race (p = 0.369) nor sex (p = 0.105) was associated with nephron-sparing surgery in univariate or multivariate analyses. Patients undergoing radical nephrectomy were more likely to have preoperative chronic kidney disease Stage 3 or later (22.5% radical nephrectomy vs 17.6% PN, p = 0.003) in univariate analysis, but significance was removed in the multivariate analysis once other covariates were included in the model. Higher pathologic T stage was associated with the use of radical nephrectomy (p < 0.001) in the univariate and multivariate analyses. Patients with pathologic T3 tumors were 69% less likely to have received PN (relative risk [RR] = 0.31, 95% confidence interval [CI] = 0.25-0.38, p < 0.001) compared with those with T1 (< 7-cm) tumors. Patients with T2 tumors were 86% less likely to have undergone PN (RR = 0.14, 95% CI = 0.10-0.20, p < 0.001) than those with T1 tumors. Recipients of PN had a slightly younger median age at diagnosis compared with radical nephrectomy recipients (60 vs 63 years old, p < 0.001) in univariate analysis, and this remained significant in the multivariate analysis. Hypertension was associated with the use of radical nephrectomy, although this lost significance in the multivariate analysis. In univariate and multivariate models, a higher CCI score (p = 0.004) was associated with the use of radical nephrectomy (Table 2).

In our analysis comparing use of minimally invasive PN (LPN or RALPN) with OPN from 2011 to 2015, after approval of RALPN, we found those undergoing surgery in later years were more likely to receive a minimally invasive approach (p = 0.001). In the univariate analysis, higher T stage (p = 0.04) and CCI score (p = 0.001), as well as hypertension (p = 0.031), were associated with an open approach, but these associations did not remain in the multivariate analysis. There were similar findings when we excluded LPN and compared only RALPN vs OPN during this same period. Certain races were more likely to receive a minimally invasive approach on univariate analysis.
This was shown in the multivariate analysis, as Asians (RR = 1.1, 95% CI = 1.05-1.21, p = 0.001) and Hispanics (RR = 1.1, 95% CI = 1.01-1.13, p = 0.028) were more likely to undergo minimally invasive PN than were whites (Table 3).

**DISCUSSION**

During the past decade, PN has become the standard treatment for most patients with T1 renal masses.\(^4,5\) In our study of patients with suspected localized RCC, nephron-sparing surgery has overtaken rates of radical nephrectomy beginning in 2012 as depicted in Figure 2. The adoption of the robotic platform has resulted in a paradigm shift in the surgical management of RCC at KPSC, with RALPN becoming the most common type of oncologic renal surgery performed in 2014. Our study serves to highlight trends in the surgical approach to RCC within an integrated health care system.

A growing body of evidence suggests that the percentage of renal parenchyma preserved during surgery is one of the most important modifiable factors predicting long-term renal functional outcomes after surgical excision of the kidney.\(^14,15\) The 2017 European Association of Urology Guidelines on RCC consider PN to be the treatment of choice for T1b (4 cm - 7 cm) RCC given the procedure’s similar oncologic outcomes and improved renal function, metabolic, and cardiovascular outcomes compared with radical nephrectomy.\(^16\) Recent studies have highlighted the increased use of PN, even in patients with T2 tumors.\(^8\) A recent

### Table 2. Partial nephrectomy (PN) vs radical nephrectomy (RN) (2009-2015)

<table>
<thead>
<tr>
<th>Patient data</th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PN (n = 1277) no. (%)</td>
<td>RN (n = 1385) no. (%)</td>
<td>p value(^a)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Median age, years</td>
<td>60</td>
<td>63</td>
<td>&lt; 0.001</td>
<td>0.99 (0.99-0.99)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>808 (63.3)</td>
<td>951 (68.7)</td>
<td>0.003</td>
<td>1.06 (0.97-1.15)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>356 (27.9)</td>
<td>434 (31.3)</td>
<td>0.051</td>
<td>0.98 (0.89-0.99)</td>
</tr>
<tr>
<td>Chronic kidney disease (CKD) stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative CKD 1/2</td>
<td>971 (62.4)</td>
<td>1012 (77.5)</td>
<td>0.003</td>
<td>0.96 (0.85-1.08)</td>
</tr>
<tr>
<td>Preoperative CKD 3+</td>
<td>208 (17.6)</td>
<td>293 (22.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>1153 (81.6)</td>
<td>720 (54.0)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>26 (2.1)</td>
<td>269 (20.2)</td>
<td>0.14 (0.10-0.20)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>T3</td>
<td>80 (6.3)</td>
<td>344 (25.8)</td>
<td>0.31 (0.25-0.38)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Race/ethnicity(^c)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>630 (49.8)</td>
<td>697 (50.6)</td>
<td>0.369</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>405 (32.0)</td>
<td>413 (30.3)</td>
<td>0.96 (0.88-1.04)</td>
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<tr>
<td>Black</td>
<td>139 (11.0)</td>
<td>176 (12.8)</td>
<td>0.84 (0.74-0.96)</td>
<td></td>
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<tr>
<td>Asian</td>
<td>91 (7.2)</td>
<td>90 (6.5)</td>
<td>0.98 (0.85-1.14)</td>
<td></td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>778 (60.9)</td>
<td>866 (64.0)</td>
<td>0.105</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>499 (39.1)</td>
<td>499 (36.0)</td>
<td>1.03 (0.96-1.11)</td>
<td>0.421</td>
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<tr>
<td>Charlson Comorbidity Index (CCI)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCI 0</td>
<td>229 (17.9)</td>
<td>132 (9.5)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>CCI 1</td>
<td>760 (59.5)</td>
<td>780 (56.3)</td>
<td>0.96 (0.82-1.13)</td>
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</tr>
<tr>
<td>CCI 3</td>
<td>186 (14.6)</td>
<td>236 (17.0)</td>
<td>0.89 (0.77-1.01)</td>
<td></td>
</tr>
<tr>
<td>CCI 4</td>
<td>229 (17.9)</td>
<td>209 (15.1)</td>
<td>0.87 (0.74-1.02)</td>
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</tr>
<tr>
<td>CCI ≥ 5</td>
<td>241 (18.9)</td>
<td>188 (13.6)</td>
<td>0.75 (0.64-0.88)</td>
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</tr>
<tr>
<td>Year of surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>130 (10.2)</td>
<td>238 (17.2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>165 (12.9)</td>
<td>234 (16.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>186 (14.6)</td>
<td>236 (17.0)</td>
<td></td>
<td></td>
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<tr>
<td>2012</td>
<td>229 (17.9)</td>
<td>209 (15.1)</td>
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<tr>
<td>2013</td>
<td>241 (18.9)</td>
<td>188 (13.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>226 (17.7)</td>
<td>191 (13.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Pearson χ² tests for independence were used for categorical variables; Wilcoxon rank sum test were used for continuous variables. Boldface values are statistically significant.

\(^b\) Based on likelihood ratio statistic. Boldface values are statistically significant.

\(^c\) Numbers for race/ethnicity do not sum to 100 because there were insufficient numbers to include those.

CI = confidence interval; RR = relative risk.
population-based study of 1836 patients from Australia has shown an increased incidence of PN for treatment of T1 RCC from 2009 to 2013.17 This was consistent with our finding of steadily increasing use of PN in our study of 5237 patients from 1999 to 2014 (Figure 2). We also demonstrated that patients undergoing PN in recent years had a younger median age at diagnosis than did those undergoing radical nephrectomy (Table 2). This difference may be attributable to the fact that younger patients are generally healthier and therefore more capable of tolerating the increased morbidity associated with PN. Additionally, there is likely more of an attempt to preserve nephrons in the younger patient.

Robotic technology and its applications to urologic surgery continue to advance, and its feasibility in advanced tumors, including those necessitating inferior vena cava tumor thrombectomy, is under investigation.18 Although randomized controlled trial data have yet to prove the oncologic efficacy of RALPN, initial oncologic outcomes after RALPN appear to be comparable to OPN, with improved perioperative outcomes. A recent study of 110 patients who underwent RALPN, with a median tumor size of 2.6 cm and follow-up of 62 months, demonstrated 5-year overall survival and recurrence-free survival of 91.9% and 97.8%, respectively.19 Perioperative outcomes for our patient population are described in a previous study by Banapour et al,12 who compared 862 patients who underwent RALPN, LPN, or OPN from 2007 to 2014 at KPSC. The authors found that, after matching for tumor complexity, minimally invasive approach was associated with less intraoperative blood loss, shorter length of stay, and less change in estimated glomerular filtration rate compared with the open approach.12 A review of 19 cohort studies comparing RALPN and OPN in a combined 3551 patients identified lower

Table 3. Minimally invasive partial nephrectomy vs open partial nephrectomy (OPN) (2009-2015)

<table>
<thead>
<tr>
<th>Patient data</th>
<th>Univariate</th>
<th>Multivariate</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>RALPN + LPN</td>
<td>OPN</td>
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<tr>
<td>Medan age, years</td>
<td>60 (n = 859, +n = 1277)</td>
<td>61 (n = 120)</td>
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<tr>
<td>Hypertension</td>
<td>536 (62.4)</td>
<td>87 (72.5)</td>
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<td>Diabetes</td>
<td>245 (28.5)</td>
<td>38 (31.7)</td>
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<td>Chronic kidney disease (CKD) stage</td>
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<tr>
<td>Preoperative CKD 1/2</td>
<td>633 (82.3)</td>
<td>86 (76.1)</td>
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<tr>
<td>Preoperative CKD 3+</td>
<td>136 (17.7)</td>
<td>27 (23.9)</td>
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<tr>
<td>Cancer stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>783 (91.8)</td>
<td>101 (85.6)</td>
</tr>
<tr>
<td>T2</td>
<td>21 (2.5)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>T3</td>
<td>49 (5.7)</td>
<td>14 (11.9)</td>
</tr>
<tr>
<td>Race/ethnicityc</td>
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<td></td>
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<tr>
<td>White</td>
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<td>Hispanic</td>
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</tr>
<tr>
<td>Black</td>
<td>96 (11.3)</td>
<td>10 (8.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>65 (7.3)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>525 (61.1)</td>
<td>68 (56.7)</td>
</tr>
<tr>
<td>Women</td>
<td>334 (38.9)</td>
<td>52 (43.3)</td>
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<td>170 (19.8)</td>
<td>13 (10.8)</td>
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<tr>
<td>CGI 2</td>
<td>503 (58.6)</td>
<td>69 (57.5)</td>
</tr>
<tr>
<td>CGI 3</td>
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<tr>
<td>CGI 4</td>
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<tr>
<td>CGI ≥ 5</td>
<td>186 (21.7)</td>
<td>38 (31.7)</td>
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<tr>
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<tr>
<td>2011</td>
<td>154 (17.9)</td>
<td>32 (26.7)</td>
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<tr>
<td>2012</td>
<td>187 (21.8)</td>
<td>41 (34.2)</td>
</tr>
<tr>
<td>2013</td>
<td>221 (25.7)</td>
<td>19 (15.8)</td>
</tr>
<tr>
<td>2014</td>
<td>205 (23.9)</td>
<td>20 (16.7)</td>
</tr>
</tbody>
</table>

* χ² tests for independence were used for categorical variables; Wilcoxon rank sum test, for continuous variables. Boldface values are statistically significant.

b Based on likelihood ratio statistic. Boldface values are statistically significant.

c Numbers for race/ethnicity do not sum to 100 because there were insufficient numbers to include those.

CI = confidence interval; LPN = laparoscopic partial nephrectomy; RALPN = robot-assisted laparoscopic partial nephrectomy; RR = relative risk.
rates of major and minor postoperative complications, lower transfusion rates, and shorter length of hospital stay in patients who underwent RALPN.20 RALPN has become increasingly utilized in our health care system since its approval and is now the most common renal oncologic surgery performed. The application of RALPN is not limited to small tumors. Results of a collaborative study of 298 patients with T2 tumors who underwent RALPN showed a 5% rate of Clavien–Dindo Grade 3 or higher postoperative complications, with acceptable renal functional and oncologic outcomes; these results suggest that RALPN can be used to treat larger tumors with appropriate patient selection.21

In our population of patients who underwent PN from 2011 to 2015, there was no association between T2 or T3 tumors and an open vs minimally invasive approach. A high CCI score was found on multivariate analyses to be significantly associated with the use of radical nephrectomy rather than nephron-sparing surgery, as well as open rather than minimally invasive approach in the PN cohort. We hypothesize that patients with more comorbidities are less capable of tolerating the increased surgical and anesthetic risks associated with nephron-sparing surgery. Interestingly, we also found an association of Asian and Hispanic race/ethnicity with the use of minimally invasive technology. However, it is important to note that this is an observational study and that there may be variables associated with geographic and ethnic variation with respect to access to a Da Vinci System. In our integrated health care system, all patients have equal access to robotic surgery.

Another limitation is that this is a retrospective study populated by data from administrative codes. Some of the surgical modality cohorts may be underpowered to identify their associations with clinicopathologic data. This could be potentially revisited in the future after accumulating more years of data to compare these surgeries. Furthermore, our study is limited by the change in procedural coding practices and the large percentage of radical nephrectomy and PN procedures performed from 1999 to 2007 of unknown approach (open vs laparoscopic). Nonetheless, this study provides insight into the current trends in renal oncologic surgery in a large population-based study within a health care system.

CONCLUSION

From 1999 to 2015, the treatment of localized RCC has changed dramatically; use of PN has increased and surpassed radical nephrectomy in 2014. In our health care system, after adoption of the robotic platform in 2011, RALPN has rapidly become the most common surgical modality (since 2014). This information may aid in the understanding of contemporary treatment options for individual patients with localized RCC. On a population level, it may shed light on the effects of clinical guidelines and introduction of a new technology on the treatment of localized RCC. 

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

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How to Cite this Article

References
Health Appraisal and the Adverse Childhood Experiences Study: National Implications for Health Care, Cost, and Utilization

Vincent J Felitti, MD, FACP

ABSTRACT

This article describes the origins of the Division of Health Appraisal in Southern California Permanente Medical Group's San Diego Department of Preventive Medicine, which provided a comprehensive and nontraditional array of preventive medicine services to more than 50,000 members a year. The fusion of Health Appraisal with the Positive Choice risk abatement services provided the origins of the now internationally recognized Adverse Childhood Experiences Study and its major implications for the outcomes and costs of medical care. The Health Appraisal system fulfilled the medical evaluation and preventive needs of most adult patients outside of the traditional and costly sickness-care system, provided rapid access to medical care, has been medically reliable and appreciated by patients, and demonstrably reduced the cost of medical care while providing each evaluated member with a comprehensive medical record in a specialized database. The unexpected resistance to this concept's further implementation deserves exploration and understanding given the current problems in medical care.

This article will discuss: Health Appraisal development and function; the Health Appraisal process; perspectives on the Health Appraisal product, outcomes, and benefits; and the Positive Choice system that linked Health Appraisal to prevention activities. A proposal for program expansion and the major economic implications of certain Adverse Childhood Experiences Study findings also will be discussed.

INTRODUCTION

“The high cost of medical care” has become a serious problem and stock phrase since the 1990s. This issue has attracted social, political, and economic attention, all of which influence current modes of practice. The relationship between the rapid rise in costs and the emergence of third-party payers has largely been overlooked, perhaps because of the practical appreciation that third-party payers probably are here to stay. Current discussion centers on how much money is spent rather than why the money is spent. “Big technology,” epitomized by the high price of magnetic resonance imaging equipment, has been cited as an explanation for the high cost of medical care. In contrast, authors of one insightful article1 argue that a more likely explanation is the heavy use of and sequelae associated with “little technology” such as blood tests and ordinary radiographs. This train of thought leads to several suggestions involving changes in physician reimbursement and education and expanded insurance incentives. Although probably desirable, these changes involve major restructuring and have no short-term effect.

This article describes a local system in the Kaiser Permanente (KP) Medical Care Program's Department of Preventive Medicine in San Diego, CA, which substantially reduced the cost of certain basic medical services. This department’s concept was an outgrowth of the famous KP Multiphasic Clinic in Oakland, CA, which was created by Morris F Collen, MD. Although its original components have been described previously, few people are familiar with the clinic’s history. In San Diego, we were able to advance Dr Collen’s impressive biomedical approach into a biopsychosocial approach and integrate patient education and major risk-abatement programs. The lack of understanding regarding these 2 KP systems is unfortunate because both deal with a basic building block of medical practice: The comprehensive medical evaluation, which is often trivialized as “a routine physical.” To reduce the enormous cost of medical care, it is useful to have a deeper understanding of the purposes, methods, and ramifications associated with these developments.

BACKGROUND: HEALTH APPRAISAL

DEVELOPMENT AND FUNCTION

The KP Medical Care Program is one of the largest private, integrated, prepaid medical systems in the world and was the prototype for health maintenance organizations. In the KP Southern California Region, 4.5 million patients are served in 12 areas, each structured around a large medical center. Although every patient ultimately is cared for in the context of an individual physician-patient relationship, we have found it appropriate to design certain practices that are distinct from those encountered in usual medical practice. This article describes a system that provides standardized, comprehensive medical evaluations to more than 50,000 adult members per year in one area of the Southern California Permanente Medical Group, and the system’s noteworthy outcomes.

The San Diego area’s Health Appraisal program began in 1975. The purpose of Health Appraisal was to provide affordable, comprehensive adult medical evaluations as a covered Kaiser Foundation Health Plan benefit. Most notably, Health Appraisal ultimately provided comprehensive medical evaluation in a nontraditional fashion to a total of 1.3 million individual members in the San Diego area over a 30-year period. Through this system we created a full, well-organized medical database for each patient, predicated on a detailed biopsychosocial history, extensive laboratory and radiographic studies, and an all-inclusive physical
examination. It has been possible to provide this basic component of medical practice at an average staffing cost that is lower than our outpatient Internal Medicine visit cost. The question at issue is whether any of this matters, and to whom.

The adult members of Kaiser Foundation Health Plan who received comprehensive evaluation through Health Appraisal ranged from healthy to chronically and complexly ill. Their average age was 57; approximately half were men. During any 4-year period, 81% of adult members older than age 26 underwent a health appraisal. Most self-selected the process, and about 20% were referred.

THE HEALTH APPRAISAL PROCESS

A comprehensive medical evaluation, or health appraisal, as performed in our Department of Preventive Medicine, was a 2-visit process with visits 2 weeks apart. At the time the initial appointment was made, our appointment system integrated certain age, sex, and risk algorithms for test selection and generated laboratory slips. We maintained an entry delay of 7 to 10 days to allow for postal delivery and completion of the detailed medical history questionnaire that was mailed to each patient’s home as the first step of the process. This questionnaire, on which further history-taking was based, included a review of all body systems; psychological questions; a family medical history; a history of past medical, surgical, and psychiatric treatment; a listing of medications; a social history including developmental life experiences during childhood; and questions about the patient’s examination-related expectations and needs. The mailing also described the process of the complete evaluation.

Visit 1

At visit 1, each patient was greeted by a receptionist. Their medical history questionnaire was collected, and they received a folder containing their preselected laboratory forms. Six patients were scheduled every 10 minutes. Following the collection of a specimen for urinalysis, patients entered an audiovisual room where they viewed a 13-minute video that described what would happen next; a physician in the video explained the significance of the tests and how to participate in unfamiliar tests like pulmonary function testing and audiometry. The video, which also provided general public health advice on topics such as immunizations and breast self-examination, was a convenient and effective means of providing information and setting mood and expectations.

The video created confidence and cooperation at the outset; it was important for us to disseminate information to patients via multiple modalities whenever possible.

After watching the video, each patient was greeted by a health assistant with whom they worked through multiple tests and measurements. These started with measurement of visual acuity followed by tonometry measured on noncontact tonometers (American Optical, Southbridge, MA). Height, weight, temperature, pulse, and blood pressure were measured. Pulmonary function was measured in the same room using a pulmonary function test device (Vitalograph, Lenexa, KS) to measure vital capacity and 1-second forced expiratory volume. Patients older than age 60 years were screened for early dementia with tachistoscope testing. Patients then proceeded to a room with individual soundproof booths where a 7-minute bilateral, full-spectrum audiogram was run on automatic recording equipment. Each patient then went to a dressing area, disrobed to the waist, and put on a gown to prepare for a chest radiograph and/or mammogram as indicated by the protocol built into the appointment computer system. Four-view mammography was performed on a 10-minute schedule. Patients then entered a small waiting area in which a new health assistant greeted them and escorted them to 1 of 7 adjacent cubicles for a blood draw and 12-lead electrocardiogram. Blood tests included total cholesterol, high-density lipoprotein, creatinine, fasting glucose, VDRL (venereal disease research laboratory) test for syphilis, thyroid-stimulating hormone, and complete blood count.

Through our universal screening program, we discovered that hemochromatosis was much more common than previously thought, and we also included measurement of serum iron and total iron binding capacity for a once-in-a-lifetime screen for this genetic disease. The appointment system tracked the completion of iron studies so the tests were not needlessly repeated during future appointments. At this point, patients had completed their first visit, and those older than age 50 years received a packet with 3 hemoccult slides to prepare at home and bring in at the second visit. In only 1 hour and 20 minutes, extensive biomedical data were collected. Six or 7 hours over several days would have been required to achieve the identical result if performed elsewhere in the same organization using conventional, nonlinear approaches; labor costs alone would have been much higher.

An assembly line environment is not ideal when working with human beings, but skillful interior design and pleasant, cheerful employees made it possible for patients to warmly accept this approach. Indeed, when 10,000 patients were surveyed via an anonymous questionnaire, “Which part of the entire process makes you most confident?” their overwhelming answer was, “The scientific tests.” By front-loading all “the scientific tests,” we fortuitously validated everything that came afterward. Interestingly, patients typically do not recognize the importance of the lengthy medical history questionnaire.

During the following week, while laboratory studies were processed, patients’ 10-page medical history questionnaires were passed through a digital scanner. “Yes” answers were organized by body system and a printout (generally 2 or 3 pages in length) was generated. A health risk analysis based on the 13 cardiovascular risk factors of the Framingham Study also was generated and mailed to each patient. This risk analysis is helpful because patients were thereby focused on relevant areas of cardiovascular significance during their second visit. Also, between visits 1 and 2, all women older than age 45 years received an informational mailing on osteoporosis prevention. Similarly, all smokers identified during appointment intake received a nonjudgmental mailing that provided information about our smoking cessation program.

Visit 2

Visit 2 centered on the physician-supervised work of a highly experienced nurse practitioner or physician assistant, each of whom performed this in-depth process approximately 2300 times.
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per year. “Yes” answers on the medical history questionnaire served to identify areas for further review. The medical history questionnaire is of particular importance because, in all of medicine, there are only 3 sources of diagnostic information: Patient history, physical examination, and laboratory studies. Whereas patients typically assume their diagnosis largely derives from laboratory test findings, experienced physicians have long recognized that about 75% of the time, diagnosis derives from patient history.

The traditional process to obtain historical information, however, is time consuming, experience dependent, and laden with interpersonal difficulties such as physicians being “too old”; “too young to understand”; or the wrong sex, race, or ethnicity for comfort. Our ability to obtain a detailed, comprehensive, highly sensitive medical history from more than 1 million patients through initial use of an inert mechanism (a paper-based questionnaire to fill out at home with information refined in the exam room) has been a pleasant surprise.

Our separate work in the Obesity Program, which led to the Adverse Childhood Experiences (ACE) Study, confirmed the importance of routinely obtaining from adults a developmental history of ordinarily unspoken adverse childhood experiences. This is best initially obtained by an inert mechanism (ie, our questionnaire, filled out at home) and later comfortably addressed in the exam room by saying, “I see on the questionnaire that…. Can you tell me how that has affected you later in your life?” We then listened, period, and implicitly accepted this person who had just told us some of his/her dark secrets. The findings from this work and their effects were unexpected and profound, and later to be described.

After reviewing the medical history questionnaire with the patient, we performed a detailed physical examination including fundoscopy, rectal and pelvic examinations, and a neurologic examination; laboratory results from visit 1 were reviewed with the patient. Predictably, the threat of false positives from screening did not materialize when results were reviewed in the context of a detailed history and physical examination. We believe that diagnostic quandaries typically are attributable to inadequate information rather than inadequate interpretation. The comment commonly attributed to William Osler remains relevant: “More diagnoses are missed by not looking than by not knowing.”

Each nurse practitioner/physician assistant examiner had 12 patient appointments scheduled per 8-hour day. Examiners worked under the guidance of supervisory physicians whose sole function was full-time, on-site supervision. The goal of this second visit was to develop a conclusive categorization of the patient as being well, at risk, or ill. If well, the patient’s evaluation process was complete. If ill, arrangements were made to see the most appropriate type of physician if there was not already an ongoing physician-patient relationship. A patient at risk for common problems was entered into one of our risk-abatement programs.

In addition to accurately describing each patient in the medical record, part of our goal has been for patients to have a general understanding of the nature of their problems and their problems’ significance. To this end, we developed a program to create and mail a summary letter several days after visit 2. This letter provided a list of diagnoses because, without the ability to describe findings by using proper terms, meaningful understanding is not possible. One or more paragraphs then explained the implications of each diagnosis and its potential treatment. The letters, which are generated by programmed extraction of explanatory paragraphs from a paragraph bank to address each specific diagnosis, cannot be distinguished from individually dictated letters and provide tangible evidence that a patient has not been lost in a large organization. The letters also can be used by patients to share information with other physicians.

The Supervisory Physician

The role of a supervisory physician in this process is the reverse of the traditional physician’s role. In a traditional medical office, the staff exists to support the physician; here, the physician exists to support and supervise the new and expanded function of the staff. The supervisory physician confirms important new diagnostic findings such as valvular heart disease and also clarifies ambiguous or important points in the medical history directly with patients, or might formulate diagnostic strategies with the examiner when a diagnosis was not evident. The physician reassured examiners and patients when necessary.

Although this process might be regarded as creating potential for fragmented care, this was avoided by our sending a copy of our records to the patient’s primary physician. For patients who were well, nothing more needed to be done. Also, substantial biomedical, psychological, and economic benefits accrued for both patients and the organization. For patients who were ill, potential fragmentation was avoided through integration into a larger coherent process. Sir James Spence stated, “The real work of a doctor is not an affair of health centers, or public clinics, or operating theaters, or laboratories, or hospital beds. These techniques have their place in medicine, but they are not Medicine.” The essential unit of medical practice is the occasion when, in the intimacy of the consulting room or sick room, a person who is ill seeks the advice of a doctor whom he trusts. This is a consultation and all else in the practice of medicine derives from it.” Generally, treatment was not initiated during the Health Appraisal process to avoid disrupting the relationship between the patient and his or her ongoing physician.

Perspectives on the Health Appraisal Product

What, then, is the product? This question needs to be addressed from 3 perspectives: The patient’s, the physician’s, and the third-party payer’s (in this instance, KP). Why do people choose to come in for a comprehensive medical evaluation when they do? Internal studies revealed that the major factor is anxiety triggered by some symptom. The concept of planned preventive maintenance motivates only about 20% of patients, typically elderly patients. Most other patients have a specific symptom and seek a complete physical examination. A medical history questionnaire item about patient expectations was helpful in this regard; it frequently indicated the reason behind the visit. We could then narrow the gap between why a patient sees a doctor and why a doctor sees a patient.

Patient Perspective

To a patient, this evaluation may thus represent sickness care. Indeed, the Department of Preventive Medicine served as an entry point to the Medical Group. Although most patients arrived
because of a specific symptom or concern and secondarily viewed the visit as preventive, they readily recognized the examination as being of value and as having a high cost in the fee–for–service sector. The health appraisal provided a portal of entry with no threshold barrier, which efficiently and appropriately directed patients on a path within a complex organization. Through the appraisal process, patients fulfilled a natural desire to receive something tangible from an insurance program. Fortunately, we have been able to accommodate this desire in a way that is affordable and mutually beneficial.

Physician Perspective
From a physician’s standpoint, Health Appraisal was seen as a case–finding mechanism for disease care. Consequently, the complete medical evaluation, a routine task that may be considered onerous in a prepaid setting (though not necessarily so in a fee–for–service setting), was removed from physicians’ responsibilities. Instead, patients with clearly defined medical problems were referred to the most appropriate physicians and arrived with an extensive and well–organized database, improving the efficiency and the effectiveness of their physicians’ efforts.

Third–Party Payer and Organizational Perspective
From the third–party payer’s standpoint, a prepaid medical system functions in contrast to a typical business in at least 1 key regard: A prepaid medical system must routinely devote its resources to the part of the business that loses money—namely sickness care, and, in particular, hospitalization. This type of system does nothing for the economically essential sector of the population that pays a substantial health care premium but does not use sickness services. This sector is the economic motor of any insurance system but ironically receives little in return. When these well, nonutilizing patients are involved in yearly membership turnover, a loss occurs. This loss is further aggravated by the retention of ill people who cannot obtain other coverage, thus creating a trend in maturing prepaid medical organizations toward a population that becomes increasingly ill. Health Appraisal affordably provides the ability to stabilize turnover in the essential healthy sector by providing these patients with a valued commodity.

From the organization’s standpoint, it is desirable to organize passage through the system from the earliest contact to improve the efficiency of utilization and to more fully understand the range and frequency of problems. This level of understanding is more likely to occur when a professional makes these decisions on the basis of comprehensive medical information and not on reports of patient symptoms. This approach can have a measurable effect on secondary costs. Moreover, this type of high–volume operation is a window through which Medical Group functions can be viewed and analyzed when quality assurance studies are desired. For example, it was easy and inexpensive to list every patient who was identified as having a chronic obstructive pulmonary disease diagnosis during the last year.

Validity and Acceptance of Health Appraisal
How do we know if an appraisal is medically reliable? To the degree that experience helps, each of our examiners performed approximately 2300 comprehensive medical evaluations each year. Also, approximately 20% of patients were physician–reviewed with examiners in the course of the day’s work, and a 10% random sample of charts was reviewed weekly. Formal and informal physician follow–up is critical to the important and difficult challenge of technical validation. On a yearly basis, each examiner videotaped at least 1 complete history and physical examination for an annual performance review. Perhaps surprisingly, patients are agreeable to participating in the videotaping process. Finally, we reviewed a small sampling of records of hospital admittances to compare the relationships of those findings to those in Health Appraisal.

The summary evaluation by more than 600 physicians in the San Diego area of the Southern California Permanente Medical Group reflected overwhelming acceptance of the Health Appraisal system, in contrast to the conceptual opposition many physicians had when Health Appraisal was in its planning stages. Sometimes people ask if a nurse practitioner or a physician assistant can perform a physical examination as well as a physician. As a categorical question, there are too many variables to make any answer meaningful. It is more meaningful to ask whether this systematic and comprehensive biopsychosocial approach to each patient via a detailed history, physical examination, and laboratory studies is as reliable as a patient’s experiences when going to a physician for a “routine physical.”

It is worth bearing in mind that an identifiable product was created, yet it is like the proverbial elephant described by 3 blind men, each of whom was palpat ing a different part of the elephant. The product is perceived differently by the patient, physician, and organization. Each viewpoint is valid but incomplete. If all 3 viewpoints are not appreciated, any preventive medicine operation probably will be regarded with hostility by some acute care physicians as they compete for scarce resources. Thus, the question “How useful is a routine physical?” is more complicated than ordinarily assumed because the vague term, “a routine physical,” is a misnomer for the comprehensive biopsychosocial medical evaluation we discuss here.

OUTCOMES AND BENEFITS
Certain benefits are dependent on a physician’s ability to function more effectively when standardized comprehensive medical information is routinely available, just as a medical organization functions more efficiently if a comprehensive electronic medical record is routinely and affordably available for each patient. Although this concept is simple to understand and easy to accept, organized efforts are necessary to ensure the integration and utilization of this new information. In the large, closed system in which we operate, it has been possible to make changes and measurements that would be difficult or unaffordable to implement in a solo practice.
We have identified substantial indicators of benefit beyond simple case findings. An early study of 700 consecutive Health Appraisal patients demonstrated an 11% reduction in their overall medical utilization for the subsequent year. This result was in contrast to the preliminary fear that, without barriers, open availability of these processes would produce overutilization. We find that accurate patient knowledge regarding their health status reduces demand, whereas uncertainty increases anxiety and demand.

Our experience in a 1979 pilot study of a 1-time contact with a temporary, onsite consultant psychiatrist supports this theory. Of 164 consecutive patients whom the consultant psychiatrist saw for a single diagnostic psychiatric interview, there was a 51% reduction in overall medical utilization the next year. The psychiatric interview was not a prelude to psychiatric referral or psychotherapy. We learned via an anonymous questionnaire that the consultation with the psychiatrist was appreciated by most patients who were involved. This 1-time diagnostic contact reduced anxious utilization by high-utilizer patients who could now recontextualize the nature of their somatic issues from being disease-related to being the result of nondisease problems. Patients also had the subtle but important experience of sharing “shameful” secrets with someone they respected without being judged.

The Adverse Childhood Experiences Study and Health Appraisal

Our department's research potential was enormous because of its high volume and standardized comprehensive medical evaluation processes. The San Diego Department of Preventive Medicine, together with Robert F Anda, MD, and the analytic team he assembled at the Centers for Disease Control and Prevention, carried out a major retrospective and 20-year prospective study of 17,337 consecutive adult KP Health Plan members going through Health Appraisal, matching their current health status against 10 categories of common but typically unspoken adverse childhood experiences that occurred approximately 50 years earlier. The links are profound and have led to international studies and trials that are starting to reshape the way primary care is provided in the western world. In brief, the ACE Study revealed an unexpectedly high prevalence of seriously traumatic life experiences during the childhoods of the 17,337 adult KP members. In more than 80 publications, we have illustrated the strong dose-response relationship decades later between traumatic early-life experiences and adult emotional states, social dysfunction, biomedical disease, and premature death.6,7

Another example of the research potential of this approach to preventive medicine was demonstrated by an analysis of 135,000 consecutive adults going through Health Appraisal in a 2.5-year period. ACE Study questions relating to traumatic life experiences in childhood had recently been added to the comprehensive medical history questionnaire that patients filled out at home. A major data mining effort revealed that the addition of these trauma-oriented questions, with follow-up in the exam room produced a 35% reduction in outpatient visits and an 11% reduction in Emergency Department visits over the following year compared with that group's prior year utilization [unpublished data]. We realized that asking, initially via an inert mechanism with later followup in the exam room, coupled with listening and implicitly accepting the person who had just shared his or her dark secrets, is a powerful form of doing. The economic implications of this 135,000-patient finding are clearly in the multibillion-dollar range for KP, Medicaid, and other large systems like the Veterans Administration. Interestingly, there has thus far been substantial resistance to further exploration or utilization of our observations, particularly as they relate to the now heavily documented prevalence of childhood sexual abuse and its long-term sequelae. The main issue may be physician discomfort in dealing with subject material like childhood sexual abuse, family violence, etc.

Inpatient and Outpatient Cost Benefits

Health Appraisal also reduced hospitalization rates. Subsequent to our initiation of routine population-wide pulmonary function testing, there was a 40% reduction in the annual number of hospital days per thousand members attributable to chronic lung disease. Health Appraisal’s abnormal pulmonary screening test findings were integrated within the Department of Internal Medicine, so any patient with abnormal findings automatically was referred to the Pulmonary Division for further evaluation. If their abnormal findings were confirmed, they were enrolled in an individualized patient education program or care with a pulmonary specialist. Our Health Appraisal case-finding cost in 1994 to identify a patient with a moderate to severe pulmonary function abnormality was extraordinarily low at $26 per case. Our first diagnostic contact with patients with advanced chronic obstructive pulmonary disease was now in the office and not the Emergency Department, which in the past had often served as a portal to hospital admission for patients in respiratory failure. Similarly, after analyzing all carcinomas of the colon discovered in 100,000 consecutive patients who completed the health appraisal, we noted a distinct shift toward Duke's A and B. Conversely, a shift toward Duke's C and D staging was associated with cases discovered through traditional practice in the Medical Group [unpublished data].

Overall, our low-cost, standardized ability to generate “big data” has barely been exploited. Because of our interest in the genetic disease hemochromatosis, we were able to affordably screen 640,000 consecutive adult patients in a multiyear period and discover 1254 clinically symptomatic but undiagnosed cases.3 Considering that lifetime treatment entails repeated phlebotomy, each of which produces a pint of economically valuable transfusable blood, the screening more than pays for itself.

The Health Appraisal Division of the Department of Preventive Medicine was highly attractive to patients and biomedically and economically productive. Patient acceptance was continually monitored with anonymous questionnaires, and we are convinced that this system operated in a way that was perceived by patients as reflecting human concern while representing the latest in medical technology. In 1998, the total staffing cost to the Medical Group for a 2-visit appraisal was approximately $100. This was less than the cost of our average internal medicine office visit, yet it provided about 2 hours of patient contact vs 20 minutes. The basis for this low cost is that a certain type of medical work was recognized as being discontinuous and infrequent in individual occurrence but high in total volume. This work was removed
from the general medical care system and brought into a parallel system that was designed to handle it and nothing else. The industrial concepts of batch processing and straight-line production have been essential, though concealed. The integration of artificial intelligence techniques, particularly with our extensive medical history questionnaire in a digital format (if completed at home over the Internet), would offer major opportunities yet to be exploited by any current electronic medical record system.

Another KP member benefit was the experimental, pre-electronic medical record creation of CompuHx, a computer system that we piloted in several examining rooms to provide real-time laser-printed digitized records of all transactions (history, physical examination, laboratory studies, and conclusions). CompuHx enabled us to provide otherwise unaffordable derivative services such as generating patient summary letters, which helped to increase patient understanding of their health status and steps for improvement. The underlying data management also allowed major data abstraction and analysis for research purposes.

LINKS TO PREVENTION: POSITIVE CHOICE

Positive Choice was the risk-abatement division of our Department of Preventive Medicine. The Positive Choice operations were a logical and necessary addition to the Health Appraisal system and had a synergistic effect. These operations provided an effective means for addressing patients who, although symptomatically well, are at increased risk for premature mortality or morbidity. Historically, these patients never fit well into the traditional medical care system and typically were not effectively handled. Positive Choice had several component programs, each of which was available to patients on a fee-for-service but nonprofit basis. Unusual within the context of our prepaid program, this method of financial operation was necessary to warrant a sufficient level of motivation among patients entering programs that essentially deal with personal behavior change. The personal effort required to bring about behavior change contrasts with the more passive role of patients seeking traditional medical treatment. The most popular Positive Choice programs (in descending order) were: Weight loss, smoking cessation, stress management, exercise, biofeedback, theatre group, body analysis, and nutrition analysis.

Weight-Loss Program

The weight-loss program was designed to help patients discover the causal underpinnings of their obesity to attain and maintain a desired weight range. Behavior change was attained through long-term participation in weekly, interactive, 2-hour small-group meetings with the same patients. Meetings were coupled with prolonged absolute fasting, a process made possible by the inclusion of a specific supplement (Optifast 70, Sandoz Nutrition, Princeton, NJ) that was essential to prevent death from prolonged absolute fasting. Our counselors in this program typically had a master’s degree or PhD in psychology or nutrition and led highly participative weekly groups covering a defined curriculum. The minimum curriculum for which a patient was admitted took 20 weeks to cover, although longer durations reflected the amount of weight patients wanted to lose. Attendance was mandatory for those who chose to enter the program. In the later years of the program, we saw radical changes take place in the treatment of obesity—the “impossible” became routine, and the emphasis shifted from major weight loss to the long-term maintenance of reliably attained major weight loss.

One counterintuitive discovery involves the emotional threat that major weight loss poses for many patients, and the fact that obesity provides many people with immediate protective benefits in the sexual, physical, and social realms despite the associated substantial long-term health risks. These discoveries and their adult relationship to previously unrecognized childhood sexual and other forms of abuse led us to create the ACE Study to ascertain and understand abuse prevalence in a general population, and the myriad ways in which these generally unrecognized experiences manifest over time.

The emphasis of our current effort in combating obesity has been to devise predictors of long-term success so patients who are likely to fail during the program can be treated differently from those who are likely to succeed. Our ability to discriminate between patients with obesity in this manner will likely be as important to their success as the ability to discriminate between patients with different types of infections. We have found that an impaired ability to express oneself assertively (as opposed to aggressively) correlates with a lack of success in behavior change. We also have found that patients who fail in the weight-loss program commonly grew up in an exceptionally dysfunctional family or were sexually abused during childhood. In the latter scenario, obesity is psychologically protective as people desexualize themselves or project an image of power through large size. Much of the difficulty associated with obesity treatment lies in the fact that, in addition to treating a long-term health risk, we are unwittingly attempting to remove a patient’s unconscious protective response to unrecognized experiences that often occurred during childhood. The information gleaned from our comprehensive medical history questionnaire, and its resultant effects, illustrates the importance of routinely seeking and gathering such sensitive information from patients.

Major weight loss can occur when prolonged absolute fasting is coupled with psychodynamic group-exploration of obesity’s origins. When starting the 20-week program, weekly medical monitoring related to absolute fasting and existing medical problems is initiated by a nurse practitioner working in conjunction with a supervisory physician. Despite the poor medical condition of some of the patients accepted into the program, it is noteworthy that there were no program-related deaths among the 30,000 patients we treated. The most weight lost by 1 person in 1 year was 277 pounds in 51 weeks. The average person completing the program lost 57 pounds in 20 weeks. Fifty percent of those completing the program have kept off two-thirds of their lost weight 18 months after the completion of the program.

A major effort that necessitates patient time, commitment, and substantial sums of money is beginning to pay off for meaningful numbers of people as we learn more about the psychodynamics underlying eating rather than focusing on teaching people to “eat right.” Moreover, inroads are being made that would not have been possible several years ago. For example, of 320 consecutive patients with type 2 diabetes who completed the program, 71% no

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Peter Sellars, noted Hollywood director and UCLA professor, is relevant: “The role of theatre, back to the time of the ancient Greeks, has been to enable people to speak about the otherwise unspeakable.” In other words, “Hey! I’m not talking about me. We’re talking about what’s up there on the stage.” An example of our theatre group results can be seen in the video, Somatization.\textsuperscript{13}

**PROPOSAL FOR PROGRAM EXPANSION**

A major opportunity exists for any medical care system to adopt the demonstrated advantages of KP San Diego’s Department of Preventive Medicine. Those familiar with the department have long felt it provided an unparalleled opportunity to showcase our best features. Our sales and marketing teams in San Diego contend that Health Appraisal and Positive Choice provided a unique marketing advantage not available elsewhere in KP’s Southern California Region.

The nature of the department and the experience we have gained by developing it to its fullest state provide the potential to create a nationwide chain of Institutes of Preventive Medicine as the banner under which KP or any large medical care system can present itself. Making these services available to the public on a fee-for-service basis, as we did on a limited scale in San Diego for longer than 3 decades, fosters excellent public relations. However, our greatest potential for economic benefit was demonstrated in the analysis of 135,000 consecutive adults going through Health Appraisal during a 2.5-year period after ACE Study questions on traumatic childhood experiences were added to the adult medical history questionnaire. The dramatic 35\% reduction in outpatient visits and 11\% reduction in Emergency Department visits during the following year have multibillion-dollar economic implications that are yet to be exploited. Unexpectedly, there has been significant resistance to making the necessary system changes to take advantage of these opportunities.

Change can be threatening. George Engel, the noted American internist-psychiatrist who developed the biopsychosocial concept of medical care wherein health and illness are understood to be consequences of the interplay of biological, psychological, and social factors attracted major interest and discussion with this concept, but a half-century later only minor change in practice has occurred even though the concept is intellectually accepted.\textsuperscript{14}

Providing these services to our members nationwide would enable KP (or any large medical care system) to uniformly apply similar health care techniques. Once these services are in place, we would have population-based data to plan the health care needs of our 12 million members and provide an accurate picture of the impact of various interventions on the prevalence of health risks. The derived data, when rendered anonymous, have substantial market value to pharmaceutical manufacturers interested in the demographics associated with their products, and to large employers who want to know more about their employees’ overall health and functionality. Lastly, such information would enable us to more easily meet the increasingly difficult HEDIS (Healthcare Effectiveness Data and Information Set) requirements.

An alternative would be to recreate the system described herein as an independent, affordable, nationwide system that would reduce medical costs while avoiding threats posed by change to the current style of medical care delivery.
CONCLUSION

Good medical care was defined by Walsh McDermott, MD, in a 1977 speech at Johns Hopkins Hospital as having 3 characteristics. First, it must be accessible; if it is not, then its quality will not matter. Second, it must be technically proficient. And third, it must perform what he termed “a Samaritan function.” Care must be provided to patients with sufficient concern in order to be psychologically acceptable and to facilitate integration between body and soul.

In serving a population of more than 500,000 KP members for more than a quarter of a century in the San Diego area, the Department of Preventive Medicine’s Health Appraisal Division usually maintained an access time of 2 weeks. Its cost was affordable to KP, especially considering the major reduction in outpatient visits. We have presented data to demonstrate the technical proficiency of the department and the strengths and benefits of the concept, and patients attest to its desirability. This systems approach is suitable for replication in any high-volume setting and offers the ideal portal of entry into our large, multispecialty Medical Group. As they pass through this portal, some members will be designated as “well,” which stabilizes the turnover of well members in a prepaid system. Others will be identified as at risk for common causes of mortality or morbidity; many of these patients will be referred to the Positive Choice risk-abatement programs. Some patients will be ill; they will be referred to the most appropriate physician with a comprehensive medical record that was inexpensively compiled. Most patients will have their needs fully met outside the traditional expensive physician-care portions of the organization, and a minority will be identified and swiftly guided to ongoing physician care.

It is difficult, if not painful, to see things in a new light. The events described here involve certain basic changes in primary care medical practice. We have successfully effected change because the changes usually involved changes in staff practice and not physician practice. Physician workload was reduced, yet new physician responsibilities were created. Findings from a comprehensive biopsychosocial medical history might require a physician to understand and address the distant psychodynamic underpinnings of diseases such as cancer being related to immunosuppression caused by unspeakable stressors such as childhood sexual abuse and other traumatic events.

In summary, it is noteworthy that after decades of productive operation, the Health Appraisal Division of the Department of Preventive Medicine was dissolved in 2003, just 2 years after the retirement of its founder. The medical evaluation work was redistributed to primary care, but the Health Appraisal practices have disappeared. This also happened to Dr. Collen’s world-famous Multiphasic Clinic in Oakland, CA, which dissolved several years after his retirement. Without question, it is easier to deal with every medical issue as though it were a purely biomedical problem rather than seeking underlying causality.

Because of the ordeals associated with any change in traditional practice, a department such as ours can encounter major pressures if it is not administratively well integrated into a traditional medical clinic. We have shown it is possible to integrate this system into an existing system of organized medical care in a way that benefits patients, clinicians, and the system. The Health Appraisal Division of our Department of Preventive Medicine introduced advanced medical practice to large numbers of patients at low cost, and served as an avenue through which to identify from large populations people who need physician attention, thus rendering available physicians more productive. Health Appraisal also offered a way to provide preventive medicine on a population basis and support the healthy subset of KP membership which functions as the economic motor to balance the financially draining aspects of any comprehensive medical practice. Our department should be regarded as a force to strengthen medical practice to the advantage of patients, society, and physicians. A nationwide chain of Institutes of Preventive Medicine could allow the KP Medical Care Program to provide a meaningful increase in services while decreasing operating costs. Opportunity awaits!

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Role of Magnetic Resonance Imaging in Diagnosis of Motor Neuron Disease: Literature Review and Two Case Illustrations

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ABSTRACT
Motor neuron diseases (MNDs) are a group of devastating neurologic disorders that cause specific damage to the motor neuron cells. The current diagnosis of MND is based on results of the clinical examination and neurophysiologic studies. The length of time of referral to a neuromuscular neurologist and the lack of validated diagnostic criteria can delay diagnosis. Although the role of imaging is currently most useful in excluding other conditions, several attempts to incorporate neuroradiology in the diagnosis of the disease and assessment of progression have shown promising results.

We conducted a literature review via searches in PubMed and The Cochrane Database using multiple relevant terms to the topic. Two cases with a challenging diagnosis of MND are described, with a thorough discussion of how the diagnosis was suggested on the basis of magnetic resonance imaging evidence in each case. Advanced magnetic resonance imaging findings can be useful tools that add to the diagnostic criteria of MNDs, especially in cases where reaching a definitive diagnosis is difficult. Such findings might enable clinicians to reach an early diagnosis that can improve the patient’s quality of life and prolong survival.

INTRODUCTION
Motor neuron diseases (MNDs) are a group of progressive degenerative neurologic disorders involving both the upper motor neurons (UMN) and/or the lower motor neurons (LMN). Major forms of MND include 1) amyotrophic lateral sclerosis (ALS), which involves both UMN and LMN; 2) primary lateral sclerosis involving mostly UMN; 3) progressive muscular atrophy involving mostly LMN; 4) progressive bulbar palsy involving both bulbar UMN and LMN only; and 5) pseudobulbar palsy.1,2 The most common disorder in the group is ALS. The diagnosis of ALS and other forms of MND is usually delayed.3 Currently, conventional and quantitative magnetic resonance imaging (MRI) are not included in the diagnostic criteria for MND and are used only to exclude MND mimics.

In this article, we review the literature and present 2 illustrative cases of possible MND that were supported by conventional and advanced MRI findings.

LITERATURE REVIEW
Etiology and Pathogenesis
The etiology and pathogenesis of MNDs are not yet well understood, and it is unclear whether the degeneration starts from the neuron cell and descends to the axons or vice versa.4 Nonetheless, extramotor cerebral pathology with certain genetic linkage is now recognized in 5% to 10% of the cases, and the rest are sporadic cases with no identified genetic component.5,6

Diagnostic Criteria
Early diagnosis of MNDs can have a major positive impact on quality of life and survival given the benefit of highly specialized palliative care and pharmacologic therapy. It is now well known that early, noninvasive positive-pressure ventilation and placement of a gastrostomy tube improves the quality of life and prolongs survival in patients with ALS.7-12 However, the subtle onset, different disease presentations, and overlapping symptoms with other neurologic disorders make early diagnosis sometimes difficult to achieve.

Several studies reported that the time from onset to diagnosis of ALS ranges from 5 months to 15 months.13 Initial misdiagnoses by general practitioners and inappropriate referrals are major reasons for the late diagnoses.14 The low incidence of ALS (median incidence rate, 2.08/100,000 population) and other forms of MNDs makes general practitioners and general neurologists unfamiliar with the variety of disease presentations.15 Multiple studies have shown that MNDs are misdiagnosed by 26% to 42% of neurologists.16-18 Even if MND is suspected, it is difficult for any clinician to tell a patient with progressive weakness or disability, or both, that their diagnosis is only probable or possible. Furthermore, with the recent approval of the intravenous medication, edaravone for the early treatment of ALS in the US19 the validation of diagnostic criteria becomes more important.

Diagnosis Challenges
El Escorial criteria and the modified version20 were developed for the diagnosis of ALS. However, the sensitivity of the criteria in the diagnosis of definite ALS is very low. It is categorized according to the presence of both UMN and LMN signs in 4 body regions: Brain stem (bulbar), cervical (neck and upper extremities), thoracic (lower back and lower extremities),21 A diagnosis of definitive ALS requires 3 regions of combined UMN and LMN pathology, probable ALS requires 2 regions of combined pathology, and possible ALS requires 1 region of combined pathology or 2 UMN signs in 2 regions.

In 2006, Awaji-shima (also called Awaji) criteria integrated electromyographic...
(EMG) data into the clinical diagnosis.22 These criteria require evidence of both acute and chronic denervation in the absence of sensory nerve conduction abnormalities and the presence of severe motor nerve conduction abnormalities. Evidence of acute denervation includes the presence of fasciculations potentials, fibrillations, and complex repetitive discharges in the weak or wasted muscle. Chronic denervation signs on EMG include increased numbers, duration, and amplitude of the motor unit potentials. A normal sensory nerve conduction study includes normal sensory nerve action potential amplitude and conduction velocities. Severe motor nerve conduction abnormalities include conduction velocity less than 75% of normal, prolonged distal compound muscle action potential latency greater than 150% of normal, and presence of more than 50% distal to proximal compound muscle action potential conduction block. Awaji-shima criteria recommended that EMG abnormalities should be considered equivalent to LMN abnormalities that increase the sensitivity for disease detection.23–24 Both El Escorial and Awaji-shima criteria are used for research purposes but are not used widely in clinical practice.

According to Traynor et al,25 56% of 388 patients given a clinical diagnosis of ALS met the definitive or probable diagnosis of ALS using the El Escorial criteria. Another 10% of the patients, who died, did not reach a level of diagnostic certainty greater than possible ALS.25 According to a meta-analysis, there was a 23% increase in the proportion of patients with a definitive or probable ALS diagnosis after using the Awaji-shima criteria that incorporated EMG findings.26 Nonetheless, there remains insensitivity in detecting the UMN pathology in MNDs, which makes their diagnosis challenging at times.27

Magnetic Resonance Imaging for Diagnosis of Motor Neuron Disease

Few studies have evaluated MRI as an additive technique that can be used for the diagnosis of MND. Findings in conventional MRI include mainly hyperintensities on the T2-weighted sequences, proton density, and fluid-attenuated inversion recovery (FLAIR) sequences along the corticospinal tract and hypointensities in the precentral gyrus, called the motor dark line, on T2-weighted images (susceptibility images).28,29 Recently, quantitative MRI techniques such as diffusion tensor imaging (DTI) have been tested and compared with conventional MRI. DTI has the potential for early detection of the micropathology of the disease before the macropathology shows up on conventional MRI.30 Although more abnormal test measures in DTI were detected in patients with ALS pathology on conventional MRI compared with patients with an ALS diagnosis without conventional MRI pathology, the studies showed variable statistical significance compared with control groups. The DTI measures did not correlate with the duration of the disease, probably because of the different disease pathologies, locations, and durations. Probably the most statistically significant DTI measures were the fractional anisotropy (FA), mean diffusivity (calculated at the motor cortex and the posterior limb of the internal capsule), and the reconstructed tractography of the cerebrospinal tract at the centrum semiovale extending to the motor cortex.31,32

Methods

We conducted an evidence-based search for relevant studies of MND using PubMed from the National Library of Medicine and The Cochrane Database of Systematic Reviews. The following search term combinations were used to find and review relevant articles in the literature: Motor neuron disease, amyotrophic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy, pseudobulbar palsy, progressive bulbar palsy, MRI, cerebral MRI, brain MRI, cervical MRI, advanced MRI, conventional MRI, diffusion tensor imaging, susceptibility weighted imaging, three-dimensional T1 imaging, T2 imaging, FLAIR, fluid attenuated inversion recovery imaging, tractography, functional MRI, Awaji criteria, El Escorial criteria, and early diagnosis. We did not apply a filter for date of publication. We reviewed all articles that discussed the role of MRI in MNDs.

This review of the literature includes 2 challenging cases for illustration. No institutional review board approval was obtained because the reported cases do not meet the criteria for human research. Both patients gave informed consent for publication without disclosure of personal information. Conventional MRI sequences included T2-weighted imaging, FLAIR imaging, and susceptibility-weighted imaging. Advanced MRI sequences were 3-dimensional T1-weighted imaging, DTI, and tractography.

CASE PRESENTATIONS

Case 1

A 63-year-old woman with a history of hypertension and adequately treated hypothyroidism presented with 6 months of progressive bilateral lower extremity weakness and difficulty swallowing. Her physical examination revealed diffuse muscle weakness in all extremities without atrophy or fasciculations. Although an up-going plantar reflex was noted on the right side, there were no clear UMN findings otherwise (normal upper extremity reflexes and absent lower extremity reflexes).

Results of the nerve conduction study demonstrated a moderate diffuse axonal polyneuropathy. The EMG study findings revealed chronic and active motor denervation out of proportion to the polyneuropathy suggestive of MND, but some diagnostic uncertainty remained because of the presence of less than 70% motor nerve conduction velocities on the nerve conduction study and the lack of any clinical history that explained such neuropathy. Because of the presence of confusing results of nerve conduction studies alongside the abnormal EMG results, the treating neurology team raised a concern of missing a treatable diagnosis such as autoimmune neuropathy.

Conventional MRI with T2-weighted susceptibility images showed a hypointense rim in the right precentral gyrus (Figure 1). The DTI results showed decreased FA in the left Brodmann area 4 (motor) and in the body of corpus callosum bilaterally with bilateral motor cortical thinning on T1-weighted 3-dimensional reconstruction (Figures 2 and 3; Table 1). When combined with EMG, the DTI findings confirmed LMN lesions. A diagnosis of MND (ie, ALS) became more likely because of the presence of both UMN and LMN lesions. A diagnosis of polyneuropathy was then extremely unlikely or irrelevant.
REVIEW ARTICLE

Role of Magnetic Resonance Imaging in Diagnosis of Motor Neuron Disease: Literature Review and Two Case Illustrations

Case 2
A 52-year-old woman presented with recurrence of bilateral lower extremity weakness 6 months after thoracic spine evacuation of syringomeningocele that had caused lower extremity myelopathy but had resolved postoperatively. She also complained of hoarseness of voice, slurred speech, difficulty swallowing, intermittent ptosis and diplopia, urinary retention, and fecal incontinence. Her physical examination revealed she had UMN findings, such as a brisk jaw jerk, hyperreflexia, and bilateral arm spasticity not explained by the conventional MRI results.

The EMG findings did not reveal new or evolving LMN changes. The possibility of primary lateral sclerosis superimposed on her other medical conditions was raised clinically but was difficult to
tease out given the confounding variables of the case. She had no evidence of other autonomic findings or orthostatic hypotension. Test results for other causes, such as myasthenia gravis, were normal.

Conventional MRI did not show any abnormality (Figure 4), but T1-weighted 3-dimensional reconstruction images displayed bilateral motor cortical thinning (Figure 5). Tractography showed asymmetric truncation of motor fibers with low FA along the corticospinal tract (Figure 6; Table 1). These findings were located in the motor cortex and extended down the corticospinal tract, indicating a selective UMN lesion. Advanced MRI results helped confirm the clinical finding of UMN pathology in 3 different anatomical regions. This abnormality was confined to the motor cortex and the corticospinal tract as illustrated in Figures 5 and 6. Absence of any lesion on the repeat conventional MRI made the correlation of her new symptoms to the old pathology (syringomeningocele) extremely unlikely. On the basis of the advanced MRI findings, the diagnosis of primary lateral sclerosis became more likely.

**DISCUSSION**

The results of the conventional and advanced MRI imaging in our 2 patients were variable but overall were consistent with dispersed UMN pathology not explained by other diseases. In Case 1, because of the presence of confusing results of nerve conduction studies (>70% motor nerve conduction velocities) with the abnormal EMG results, the treating neurology team considered the possibility of missing a treatable diagnosis such as autoimmune neuropathy. Eventually, the MRI results confirmed degeneration along the fibers of the corticospinal tract and the motor cortex, thus increasing the possibility of an ALS diagnosis.

In Case 2, because this was a challenging case, the neurology team suggested using other advanced modalities to try to narrow the differential diagnosis. Although the patient’s symptoms were anatomically overlapping, a chronologic understanding of her symptoms was crucial. Initially, the patient had lower extremity myelopathic manifestations with EMG degenerative changes. This condition resolved after surgery. The patient came back describing new progressive myelopathic manifestations involving the lumbar, cervical, and bulbar regions without LMN signs that started 6 months after resolution of her initial symptoms. A subsequent spine MRI revealed no new lesions. A repeat EMG showed resolution of the denervation signs. Findings on advanced MRI sequences suggested that a diagnosis of primary lateral sclerosis was more likely.

Although a retrograde atrophy of the corticospinal tract secondary to a thoracic syrinx was a possibility, it was rather unlikely given the long period of resolution of the lower extremity symptoms and resolution of signs of denervation on the EMG after surgery, with no evidence of new lesion on the most recent MRI. Nonetheless, it was even less probable that the developmental abnormalities that caused the thoracic syrinx initially might be causing her new symptoms because the patient was asymptomatic in the bulbar and cervical region before the development of the thoracic syrinx and because the new MRI did not show any lesion progression.

A similar diagnostic approach was followed by Matsunaga et al32 before they diagnosed ALS in a patient with new-onset myelopathic weakness in the upper extremities. In their case, it was accompanied by C4 to C7 spinal foraminal narrowing.

Primary lateral sclerosis presents early with only UMN signs; LMN signs appear several years later. For this reason, diagnosis in the early stages depends on the absence of LMN signs. The disease is slowly progressive. Such challenges make the diagnosis difficult for many clinicians, which might contribute to the reported rarity of the disease. The diagnosis of primary lateral sclerosis is thus mainly clinical so far, making it likely a diagnosis of exclusion.

Other diagnoses that need to be excluded in patients with primary lateral sclerosis are diffuse neurodegenerative diseases, including multiple system atrophy and spinocerebellar ataxia. These possibilities further stress the importance of MRI, which in our Case 2 did not show diffuse cerebral or cerebellar atrophy. Clinically, multiple system atrophy was less likely in our case because of the absence of orthostatic hypotension that indicates autonomic instability, and spinocerebellar ataxia was less likely because of the absence of ataxia.

Although MNDs involve pathologies in both the UMN and LMN with variable degrees of involvement, it is unknown which pathology occurs first. Is it an anterograde process starting as neuropathy and spreading downstream,

### Table 1. Comparative fractional anisotropy across different sites of corticospinal tract from cortex to medulla*

<table>
<thead>
<tr>
<th>Site</th>
<th>Patient 1 Left</th>
<th>Patient 1 Right</th>
<th>Patient 2 Left</th>
<th>Patient 2 Right</th>
<th>Reference value $^{3, 11}$</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA 4 (motor)</td>
<td>0.65</td>
<td>0.64</td>
<td>0.65</td>
<td>0.64</td>
<td>0.69</td>
<td>0.68</td>
</tr>
<tr>
<td>BA 3, 2, 1 (sensory)</td>
<td>0.65</td>
<td>0.64</td>
<td>0.65</td>
<td>0.64</td>
<td>0.69</td>
<td>0.68</td>
</tr>
<tr>
<td>Posterior limb of internal capsule</td>
<td>0.65</td>
<td>0.64</td>
<td>0.65</td>
<td>0.64</td>
<td>0.69</td>
<td>0.68</td>
</tr>
<tr>
<td>Midbrain</td>
<td>0.72</td>
<td>0.70</td>
<td>0.62</td>
<td>0.60</td>
<td>0.70</td>
<td>0.68</td>
</tr>
<tr>
<td>Pons</td>
<td>0.69</td>
<td>0.67</td>
<td>0.63</td>
<td>0.60</td>
<td>0.70</td>
<td>0.68</td>
</tr>
<tr>
<td>Medulla</td>
<td>0.27</td>
<td>0.35</td>
<td>0.27</td>
<td>0.35</td>
<td>0.28</td>
<td>0.29</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.80</td>
<td>---</td>
<td>0.79</td>
<td>---</td>
<td>0.78</td>
<td>0.29</td>
</tr>
<tr>
<td>Splenium of corpus callosum</td>
<td>0.47</td>
<td>0.30</td>
<td>0.72</td>
<td>0.83</td>
<td>0.70</td>
<td>0.29</td>
</tr>
<tr>
<td>Body of corpus callosum</td>
<td>0.47</td>
<td>0.30</td>
<td>0.72</td>
<td>0.83</td>
<td>0.70</td>
<td>0.29</td>
</tr>
</tbody>
</table>

*In Patient 1, there is a decrease of the FA in the left motor cortex and the body of the corpus callosum bilaterally. In Patient 2, there is a significant decrease of the FA in the brain stem bilaterally.

$^{3}$Boldface values indicate significant decreases in fractional anisotropy (FA).

$^{a}$Italic values indicate mild decreases in FA.

BA = Broadmann area.
or is it a retrograde process starting as axonopathy and then extending upstream to the motor neuron? It is possible that both hypotheses are true and that different or combined forms of the disease occur. Also, the anatomical location where the disease begins is still unknown. Nevertheless, other motor areas such as the corpus callosum, especially the middle and posterior parts, are involved in the pathology and are now well recognized. A new hypothesis in the pathogenesis of the disease has been proposed, which suggests an imbalance between the excitatory-inhibitory signals in the interneuron on the basis of some magnetic resonance spectroscopy studies.

DTI is a promising quantitative MRI technique for the diagnosis of MND. This technique detects the diffusion of proton particles freely within the tissues in multiple planes while intact myelin provides the maximum restriction of such diffusion, leading to a higher FA and lower mean diffusivity. Decreased FA and increased mean diffusivity in the cerebrospinal tract in primary lateral sclerosis, ALS, and progressive muscular atrophy could potentially be used as a marker for early and clinically silent UMN involvement. Inconsistent mean diffusivity values in some studies might be attributed to coexisting gliosis along with myelin/axon degeneration that also can limit proton diffusivity. If this is true, normal mean diffusivity and decreased FA might indicate longer duration of the disease because of restrictive gliosis. Decreased FA also has been described in the corpus callosum, premotor white matter, prefrontal white matter, temporal white matter, and cortical cord. Nevertheless, a significant direct correlation between the amount of decrease in FA and disease progression has been noticed in small studies. The amount of corpus callosum involvement was independent of the degree of UMN involvement clinically in these small studies, and other studies showed truncated subcortical motor fibers on tractography.

Changes on magnetic resonance spectroscopy such as decreased N-acetylaspartate (NAA), NAA/creatine, NAA/choline, NAA/creatinine + choline, and NAA/myoinositol along the cerebrospinal tract from the cortex to the cerebral peduncle have been described with variable sensitivity and specificity. These changes also correlated with the disease severity. The NAA/myoinositol marker is the most sensitive and specific.

Three-dimensional T1-weighted reconstructed MRI images have shown cortical thinning in the primary motor cortex with or without clinical cognitive impairment. Also, temporal and parietal thinning has been described in patients with associated dementia and possible genetic linkage. Results using a surface-based rather than voxel-based technique were more statistically consistent with these findings. A small, controlled study in 2016 showed no difference in cortical thickness or DTI metrics between patients with LMN–predominant MND and healthy controls. Cervical spinal cord MRI showed evidence of thinning of the cord diameter compared with controls. Also, a decrease in the FA on DTI was noticed, especially in the distal cervical cord. Assessment of the cervical cord requires more sophisticated MRI machines and is technically challenging to assess in most medical centers.

Regarding functional MRI, a few studies have shown decreased connectivity in the sensorimotor areas, but other study results showed increased connectivity. This is probably because it depends on the type of neuron affected and the timing along the disease course when the functional MRI was done. The increased connectivity might be caused by a compensatory process for the associated structural damage or because of direct loss of the inhibitory interneurons. It is important to note that the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of advanced MRI findings have not been studied on a large scale. Nonetheless, incorporating such findings with the current diagnostic criteria and studying its effect on shortening the time needed to reach a diagnosis of MND and on outcomes must be studied as well. Because the electrophysiologic results to the LMN clinical criteria for MND diagnosis has improved the sensitivity of the criteria, it is possible that neuroimaging might add to the sensitivity of detecting UMN pathology.

According to the revised criteria of the World Federation of Neurology Research Group on Motor Neuron Diseases, conventional MRI studies are not required in patients with clinically definite disease with bulbar or pseudobulbar onset. However, in those with probable or possible ALS, routine brain and/or spinal cord MRI can be useful in excluding several ALS mimics.

According to the European guidelines, and although cerebrospinal tract hyperintensities or a T2-weighted hypointense rim in the precentral gyrus can support a preexisting suspicion of MND, the specific search of these abnormalities for the purpose of making a firm diagnosis is not recommended. We encourage the establishment of new clinical trials using the different MRI measures to gain additional insight into disease pathophysiology and into the value of these techniques in a longitudinal assessment of the diagnosis and progression of MNDs.

CONCLUSION

As illustrated in our 2 challenging cases, findings on the conventional MRI sequences (T2-weighted imaging, FLAIR imaging, and susceptibility-weighted imaging) and advanced MRI sequences (3-dimensional T1-weighted imaging, DTI, and tractography) solidified the MND diagnosis. The intent of this review is to raise the awareness of these advanced MRI findings to serve as a backup tool when a diagnosis of MND is in doubt.
By having these tools available, the time to reach a definitive or more affirmative diagnosis can be shortened in doubtful cases. Although it is not the intent of this article to change the guidelines or amend the diagnostic criteria, our results point toward the need for more advanced criteria for the diagnosis of MNDs.

Applying early supportive measures and pharmacologic therapies will improve the quality of life and survival in patients with MNDs, and thus early diagnosis is preferable. Primary care practitioners and general neurologists may have limited experience with MNDs, and a delay in diagnosis may lead to worse outcomes. Recent studies and reviews have shown that a combined approach between all imaging techniques (especially DTI and functional MRI) might have stronger sensitivity and specificity. Nevertheless, we recommend the development of standardized criteria that include clinical findings, EMG findings, and MRI findings to increase the sensitivity of disease detection.

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

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References
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What Use Is It?

For the doctor, whether it is sad or not is not the issue. Let the patient live in illusions to the end . . . it is humane and the best way . . . . We are sometimes reproached for conducting incessant studies on the major neurologic diseases, which have, up to now, mostly been accurate. What use is it? . . . Let us keep working, in spite of everything. Let us keep searching.

—Jean-Martin Charcot, 1825-1893, French neurologist and professor of anatomical pathology
This photograph is part of a series taken in remembrance of the worst wildfire in California history. These images were taken in the community around the Santa Rosa Medical Center.

Dr Chen is Medical Director and a Pathologist at the Santa Rosa Medical Center in CA. More of Dr Chen’s photographs can be seen on the cover and page 90 in this issue of The Permanente Journal.
Osteonecrosis of the Hip: A Primer

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ABSTRACT

In this report, we deliver a concise and up-to-date review of osteonecrosis, a pathologic, painful, and often disabling condition that is believed to result from the temporary or permanent disruption of blood supply to an affected area of bone. We will discuss the epidemiology (disease distribution), pathogenesis (mechanism of development), etiology (associated risk factors, causes, and disorders), clinical manifestations (reported symptoms and physical findings), diagnosis and classification, and treatment options for hip osteonecrosis.

INTRODUCTION

The intent of this article is to present an update on osteonecrosis (ON) affecting the femoral head or hip joint and how it can best be managed in the adult population. Specifically, this report will encompass the epidemiology, pathogenesis, etiology, clinical manifestations, diagnosis and classification, and treatment options for hip ON. ON, also referred to as avascular necrosis, aseptic necrosis, or ischemic bone necrosis, is associated with many disorders and risk factors that cause mature bone cells to die, leading to bone destruction (e.g., collapse) or end-stage arthritis of the femoral head. The condition can occur in any bone in the body (e.g., upper extremity, knees, shoulders, and ankles), or in more than 1 bone at different times, but it most commonly affects the hip joint. When initially diagnosed in an area other than the hip, the hip should simultaneously be evaluated clinically and with radiographic and other imaging studies. The causes of ON are classified as either traumatic (related to an injury) or atraumatic (not related to an injury). Accurately diagnosing and classifying ON are important in helping to direct treatment options. Identification of associated risk factors and patient education are important in successful management of ON. Targeting associated risk factors, pharmacologic management, and/or surgery, including joint preserving procedures and total hip arthroplasty (THA), also play significant roles in the clinical care of patients with ON.

EPIDEMIOLOGY OF HIP OSTEO NECROSIS

Although the exact prevalence of ON is unknown, the incidence is estimated to be between 20,000 to 30,000 newly diagnosed patients each year in the US. ON is the underlying diagnosis in approximately 10% of all THA patients in the US. ON affects people of all ages, although it is most commonly seen in patients between the ages of 30 and 65 years. The mean age at diagnosis is typically younger than age 50 years. The male-to-female ratio varies depending on the associated comorbidities. For example, alcohol-associated ON is more common in men, whereas ON associated with systemic lupus erythematosus (SLE) is more common in women. More than 20,000 people each year require hospital treatment for hip ON. In many of these cases, both hips are affected by the condition. Most commonly, ON affects the proximal end (epiphysis) of the femur (hip bone).

PATHOGENESIS OF HIP OSTEO NECROSIS

The mechanism(s) by which hip ON develops remains unclear. For the most part, hip ON is believed to result from the combined effects of genetic predisposition, metabolic factors, and local factors affecting blood supply including vascular damage, increased intravascular pressure, and mechanical stress. Most experts agree that a lack of blood supply to the femoral head and bone marrow, which produces stem cells and platelets, causes death of the osteocytes (cells within mature bone) and/or mesenchymal cells (stem cells that form cartilage, bone, and fat). The result is demineralization or resorption of the dead tissue by new but weaker osseous tissue (trabecular thinning), subsequently leading to subchondral fracture and collapse of the femoral head.

ETIOLOGY OF HIP OSTEO NECROSIS

A combination of traumatic and atraumatic factors can directly contribute to the etiology of ON (see Sidebar: Etiologic Factors Associated with Osteonecrosis). On the basis of longitudinal cohort studies and meta-analyses, direct risk factors have been discovered that play a definitive etiologic role in the development of ON. Associated risk factors, however, account for most of the links to the eventual development of ON.

Traumatic Causes of Hip Osteonecrosis

Traumatic causes of ON include femoral neck fractures or dislocations as well as direct injury of bone or marrow elements (e.g., related to radiation injury, dysbarism, or Caisson disease). The mechanism involved in femoral neck fractures or dislocations is damage to the extraosseous blood vessels, which results in disrupted blood supply to the affected region of the hip. Hip dislocation is another type of traumatic injury, which affects approximately 20% of trauma-related ON patients.
Caisson disease (e.g., decompression in scuba diving) causes the formation of nitrogen bubbles that can occlude arterioles, leading to ON. Patients who develop symptoms can develop hip ON years after exposure to this process. The depth and duration of pressure and number of exposures are important factors in the progression of this disorder.

**Atraumatic Causes of Hip Osteonecrosis**

Numerous studies report prolonged use of corticosteroids associated with the development of ON can be directly related to duration and total dosage of the medication. Patients treated with prolonged high doses of glucocorticoids appear to be at greatest risk for developing ON; however, these patients often have multiple risk factors.

Glucocorticoid-induced ON develops in 9% to 40% of patients receiving long-term therapy, and develops much less frequently in patients receiving short-term therapy. One meta-analysis and systematic review identified an incidence of ON in nearly 7% of patients who used < 2 g of corticosteroids. From this meta-analysis, a lower risk was seen in patients treated with doses of prednisone less than 15 mg/d to 20 mg/d. One population-based study of 98,390 patients showed the incidence of hip ON among patients who had received a single short-term, low-dose methylprednisolone taper pack was 0.13%, compared with 0.08% in patients who were not prescribed a methylprednisolone taper pack, thus indicating a number needed to harm of 2041 patients.

Alcohol use has been associated with approximately 31% of patients who develop hip ON. Excessive alcohol consumption related to ON of the hip is believed to result from the decreased bone mass caused by excess lipid formation and increased intracellular lipid deposits, leading to osteocyte death and ON.

High doses of corticosteroids and excessive alcohol use together present the highest associated direct risk factors for the development of hip ON and account for more than 80% of cases not related to trauma. One study compared 112 patients who had idiopathic hip ON and no history of systemic corticosteroid use with 168 controls. An elevated risk for regular alcohol drinkers and a clear dose-response relationship with alcohol use were noted, compared with controls. The relative risks were 3.3, 9.8, and 17.9 for current drinkers of less than 400 mL/wk, 400 mL/wk to 1000 mL/wk, and more than 1000 mL/wk of alcohol, respectively.

ON is common in patients with sickle cell disease because of its propensity to cause red blood cell sickling and bone marrow hyperplasia. Approximately 50% of affected patients develop ON by the age of 35 years. Sickle cell hemoglobinopathy can directly cause vascular obstruction and ON.

The development of ON has been reported in 3% to 30% of patients with SLE, and those most at risk are patients who have taken glucocorticoids with regular doses of prednisone greater than 20 mg/d. ON has been reported in as many as 60% of patients with Gaucher disease (a hereditary disorder) because of its ability to directly obstruct vascular supply. Gaucher disease is an autosomal recessive inherited disorder of metabolism where a type of fat (lipid) called glucocerebroside cannot be adequately degraded. Normally, the body makes an enzyme called glucocerebrosidase (a normal part of the cell membrane) that breaks down and recycles glucocerebroside.

Other less common but apparent links to hip ON include patients with antiphospholipid antibodies, Cushing disease, and SLE. The development of acute lymphoblastic leukemia, chronic myeloid leukemia, and acute myeloid lymphoma places patients at increased risk for ON related to the treatment with steroids for these conditions.

Pancreatitis (usually associated with use of corticosteroids), pregnancy, chemotherapy, smoking, vasculitis, pleuritis, and central nervous system factors such as an inflammatory response resulting in a reduction in the number of sympathetic nerve fibers (as seen in rheumatoid arthritis, Crohn disease, Charcot foot, and inflammatory bowel disease), have been associated with ON.

There is some evidence that hip ON may have a genetic basis underlying associated risk factors. For example, men are affected as much as 3 times more than women when excessive alcohol use is the associated risk factor. However, when lupus or corticosteroid use are the associated risk factors, women are affected more often than men. This increased susceptibility may be made possible, at least in part, owing to differences related to hormones and sex chromosomes. Chronic renal failure or end-stage renal disease in patients on hemodialysis, hyperuricemia/gout, HIV infection, hyperlipidemia, organ transplantation, and intravascular coagulation are also linked to the development of ON. Despite the many possible associations and links, an estimated 20% of ON cases are labeled as idiopathic or of unknown etiology.
CLINICAL MANIFESTATIONS OF HIP OSTEONECROSIS

Hip pain is the most commonly reported symptom of later-stage ON, although a small proportion of patients may not have symptoms. Pain in the groin is the most commonly reported symptom, followed by pain referred into the thigh and buttock. Pain can present with weightbearing or joint motion. Pain at rest occurs in approximately two-thirds of patients with ON, and pain at night occurs in approximately one-third of patients. Pain in multiple locations of the body is rare and suggests a multifocal process. Physical findings of hip ON are generally nonspecific but may entail reduced range of motion of the affected joint, painful ambulation, Trendelenburg sign, and/or crepitus.

Clinical Assessment of Hip Osteonecrosis

ON of the hip is generally addressed by 1) review of a patient’s medical history, 2) obtaining appropriate radiologic evaluation, 3) determining the stage of the condition, and 4) developing a plan for treatment options. When evaluating a patient for ON, questions should be directed at assessing a history of pain, use of medications (especially corticosteroids), surgery, pregnancy, trauma, chronic medical conditions (especially sickle cell disease, Gaucher disease, autoimmune disease, and leukemia), smoking, and/or alcohol use. When asking about injuries/illnesses, it is important to carefully explore injuries related to hip fractures, dislocations, or scuba diving because Caisson disease is atraumatic.

DIAGNOSIS AND CLASSIFICATION OF HIP OSTEONECROSIS

Diagnosing hip ON in the initial stages of the disorder is important for management; at initial stages, the disease may not progress. In most cases, patients with early-stage ON are generally without symptoms and are identified incidentally; unfortunately, most patients do not present for evaluation until the ON has reached later stages. Although there is presently no definitive treatment known to permanently halt ON from progressing to later stages, there are treatment methods, such as lipid lowering agents, anticoagulants, and bisphosphonates, currently being used for this purpose.

A diagnosis of ON can accurately be made when a patient is symptomatic, imaging findings are compatible, and other causes of pain and bony abnormalities either are unlikely or have been excluded. Beyond the clinical and physical examination, imaging techniques such as radiographs and magnetic resonance imaging (MRI) scanning are also used for diagnosis. Plain radiographic evaluation is performed first, followed by MRI. MRI has been reported to be >99% specific and sensitive for detecting early ON. MRI images can also quantitatively assess the size of the lesion or involvement of the affected bone by digitizing the area of involvement of the femoral head occupied by bone with abnormal texture. MRI changes include well-demarcated and homogeneous focal lesions on T1-weighted images with a single-density line separating normal and ischemic bone, as well as a second high-intensity line on T2-weighted images (the pathognomonic double-line sign) representing hypervascular granulation tissue. This level of imaging detail is useful because the size and extent of the lesion of the affected bone is important and can help direct treatment. For end-stage disease, however, use of MRI in patients with ON may be unnecessary because treatment options at this stage can be limited.

These findings are often classified using the 4-stage Ficat and Arlet classification system, which is described here and in Table 1. The plain radiograph can remain normal for months after the onset of symptoms such as groin pain (Stage I). The earliest radiographic findings are usually mild density changes, followed by sclerosis and cysts (Stage II). Findings then progress to the pathognomonic crescent sign (subchondral radiolucency seen in the anterolateral aspect of the proximal femoral head) from subchondral collapse (Stage III), and subsequent loss of sphericity (measurement of the roundness) or collapse of the femoral head with eventual joint-space narrowing and

Table 1. Ficat & Arlet classification system of the femoral head

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clinical</th>
<th>Radiographs</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>No symptoms; preclinical</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Possible groin pain</td>
<td>Normal or mild osteopenia</td>
<td>Possible edema</td>
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<tr>
<td>Stage 2</td>
<td>Groin pain and stiffness; pain with activity</td>
<td>Osteopenia and/or subchondral cysts; diffuse porosis; precollapse of joint space</td>
<td>Outlines area of involvement of the femoral head</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Groin pain, stiffness, radiation of pain; pain with activity</td>
<td>Crescent sign and/or subchondral collapse (flattening) of joint with secondary degenerative changes; loss of sphericity of femoral head</td>
<td>Same as radiographs</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Groin pain and limp; pain at rest</td>
<td>End-stage disease with collapse; extensive destruction of joint; reduced joint space</td>
<td>Same as radiographs</td>
</tr>
</tbody>
</table>

MRI = magnetic resonance imaging

Figure 2. Progression of osteonecrosis using the Ficat & Arlet classification system. Osteonecrosis can progress from a normal, healthy hip (Stage I) to the collapse of the femoral head (Stage IV).
Degenerative changes in the acetabulum that are visible (Stage IV). Key radiographic features to look for include 1) stage (precollapse vs postcollapse), 2) size of lesion, and 3) amount of head depression.

A computed tomography scan producing a 3-dimensional picture of the bone has moderate sensitivity but is nonspecific and can pose a significant radiation burden to patients. Computed tomography can have some specificity if there is already femoral head collapse. Fortunately, most clinicians are assured with their diagnosis of ON without computed tomography scanning, which is generally reserved for distinguishing precollapse and postcollapse disease.

Differential Diagnosis of Hip Osteonecrosis

Because patients with symptomatic hip ON can present with symptoms similar to many other hip pathologies, these should be adequately ruled out before final diagnosis. Bone marrow edema syndrome and subchondral fractures are two of many potential diagnoses that need to also be considered.

Bone marrow edema syndrome, also known as transient osteopenia of the hip, may occur in isolation or in association with injuries, particularly those that result in neurologic damage. In the latter situation, chronic pain and transient osteopenia are features of the complex regional pain syndrome (also known as reflex sympathetic dystrophy, causalgia, and other terms). Bone marrow edema syndrome can be differentiated from ON on the basis of histologic and MRI findings.

Subchondral fracture of the femoral head typically occurs in patients with preexisting osteopenia and is generally thought to represent an insufficiency fracture. These fractures may be difficult to visualize with plain radiographs. Subtle flattening is sometimes present with early lesions; collapse of the femoral head is progressive.

Clinical Management of Hip Osteonecrosis

Factors to consider when developing an optimal management approach for symptomatic ON of the hip should be aimed at treating the stage and degree of involvement of ON, the extent and location of bony involvement, the presence (or absence) of symptoms, and the patient’s comorbidities. The goal of therapy is to preserve the biological hip joint for as long as possible while also taking into consideration quality of life issues such as patient age, mobility, occupation, and lifestyle. Three main therapeutic options for management of hip ON include 1) nonoperative management, 2) joint-preserving procedures, and 3) THA.

The effects of atraumatic causes of hip ON pose special concerns. For those affected, 67% report no symptoms but may eventually go on to have a collapsed joint. The natural history of asymptomatic medium-sized, and especially large, osteonecrotic lesions is progression to worsening of the condition and eventually end-stage disease and collapse of the hip in a substantial number of patients. For those with symptoms, approximately 80% to 85% of cases will result in collapse of the femoral head within 2 years. Early diagnosis of ON may therefore provide the opportunity for early treatment, which can prevent collapse and, ultimately, the need for total joint arthroplasty. However, most patients present late in the course of the disease, and a high index of suspicion is necessary for those with known or probable risk factors, particularly patients with high-dose corticosteroid use.

Similarly for patients with asymptomatic hip ON, the size, extent, and location of the necrotic lesion affecting the femoral head should be considered. Generally, lesions affecting less than 15% of the femoral head are best managed nonoperatively; lesions between 15% to 30% should be managed surgically; and lesions involving more than 30% of the femoral head are likely to progress to collapse, despite surgical intervention, and eventually require THA.

Nonsurgical Treatment Options in Hip Osteonecrosis

Physical Therapy

Physical therapy may provide relief and alleviate some symptoms but generally will not preclude progressive hip ON from advancing to later stages. Similarly, restricting weight-bearing with the use of assistive devices such as crutches or a cane may be useful to control symptoms of pain, weakness, and antalgic gait. Physical therapy is not appropriate if the goal of treatment is to prevent the hip from requiring THA, and to date there is no evidence that weight-bearing restrictions are helpful in preventing progressive ON disease from advancing to end-stage disease.

Medications

Nonsteroidal anti-inflammatory drugs and acetaminophen may provide temporary relief of pain in symptomatic patients. Opioid medications may be used judiciously and for short periods of time when other agents are ineffective to manage moderate-to-severe pain while surgical options are being considered.

Investigational medication options currently being used but that are not proven or reliably used to treat ON include 1) anticoagulants, 2) bisphosphonate antiresorptive agents, 3) cholesterol lowering statins, and 4) hyperbaric oxygen.

Surgical Options in Early-Stage Hip Osteonecrosis

Core Decompression

Core decompression is a minimally invasive surgical technique performed to manage symptoms in early stages (precollapse) of the condition (eg, Ficat and Arlet Stages I and II). The procedure involves drilling holes into the femoral head to relieve pressure and create channels for new blood vessels to nourish the affected areas. The published success rates of core decompression vary greatly from 40% to 100%, depending on patient population. Higher success rates after core decompression are seen in patients with the earliest disease stages. Patients with successful core decompression procedures typically return to unassisted ambulation after several months and can have complete pain relief.

Bone Grafting

Core decompression can be combined with bone grafting to help regenerate healthy bone and support cartilage at the hip joint. A bone graft is healthy bone tissue that is transplanted to the area of necrotic or dead bone. A standard technique uses an autograft that involves taking bone from one part of the body and moving it to another part of the body. A bone graft that is harvested from a donor or cadaver is called an allograft and is typically acquired through a bone bank.
Etiologic Factors Associated with Osteonecrosis

**Traumatic-associated risk factors**
- Femoral neck fracture
- Dislocation or fracture-dislocation
- Sickle cell disease
- Hemoglobinopathies
- Caisson disease (dysbarism)
- Gaucher disease
- Radiation

**Atraumatic-associated risk factors**
- Corticosteroid administration
- Alcohol use
- Systemic lupus erythematosus
- Cushing disease
- Hypersecretion of cortisol (rare)
- Chronic renal failure/hemodialysis
- Pancreatitis
- Pregnancy
- Hyperlipidemia
- Organ transplantation
- Intravascular coagulation
- Thrombophlebitis
- Cigarette smoking
- Hyperuricemia/gout
- HIV

**Other potential risk factors**
- Idiopathic causes

**Surgical Options in Advanced-Stage Hip Osteonecrosis**

**Vascularized Bone Graft**
A vascularized fibula graft is a more involved surgical procedure in which a segment of bone is taken from the fibula with its blood supply. The graft is then transplanted into a hole created in the femoral neck and head, and the artery and vein are reattached to help heal the area of ON. A recent review reports this procedure to have a clinical success rate ranging from 36% to 90%.

**Nonvascularized Bone Graft**
There are 3 types of nonvascularized bone grafting surgeries: 1) trapdoor procedure, 2) lightbulb technique, and 3) Phemister technique. The trapdoor procedure is one in which autogenous cancellous and cortical bone grafting have been successful in Ficat and Arlet Stage III hip ON in patients with small- to medium-sized lesions. A review of the results of 30 trapdoor operations performed on 23 patients with Ficat and Arlet Stage III or Stage IV ON of the femoral head performed through a so-called trapdoor made in the femoral head revealed a good or excellent result as determined by the Harris Hip Score system. Surgical options have longevity restrictions—components wear after long-term use—these patients will likely require a revision THA later in life.

**Phemister Technique**
In the Phemister technique, a trephine is inserted through the femoral neck to create a tract to the lesion. A second trephine is then inserted to create another tract to the lesion site. A cortical strut graft can then be placed in the lesion. A recent review reports this procedure to have a clinical success rate ranging from 36% to 90%.

**Total Hip Arthroplasty**
Once the femoral head has undergone major collapse, replacing the hip joint is the only practical operative option and offers the most predictable pain relief in advanced ON. THA is successful in relieving pain and restoring function in the majority of patients. In THA, the diseased cartilage and bone constituting the hip joint is replaced with artificial implants made of metal and plastic. A prosthetic hip replacement generally lasts 15 years before it might wear out and need to be revised. For the younger age group, a THA may be a suboptimal solution because of possible activity restrictions. Additionally, because prostheses have longevity restrictions—components wear after long-term use—these patients will likely require a revision THA later in life.

**PATIENT EDUCATION**

**ABOUT HIP OSTEONECROSIS**

**Prevention of Osteonecrosis**
Patient education about risk factors, therapies, and management is essential for patients to make better-informed decisions about their condition. The process of ON education involves identification of an individual’s associated disorders and risk factors related to ON.

Patients with asymptomatic ON may have a high prevalence of progression to symptomatic disease and femoral head collapse. Education for patients with asymptomatic disease is precautionary and imperative to ensure modification of risk factors and optimization of care. Preventing atraumatic ON requires 1) avoiding excessive use of alcohol defined as < 15 drinks/wk for men and < 8 drinks/wk for women, 2) avoiding smoking, and 3) reducing corticosteroids to the lowest tolerable dose.
possible therapeutic dose. Informing patients about the correlation between corticosteroid use and potential development of ON is critical in management of this condition.

Prevention of Progression of Osteonecrosis

Patients diagnosed with early-stage ON should be advised of the aforementioned precautions and should avoid placing excessive pressure on their joints, follow a healthy diet, and maintain an appropriate weight to mitigate progression of ON. Although a healthy diet in itself does not directly reduce pressure on a patient’s joints, weight loss (if overweight/obese) will reduce axial loads on the hip joint, which in turn decreases the strain applied to the femoral head/neck (to both the tension and the compression sides).  

CONCLUSION

ON is a pathologic and often painful condition involving necrotic areas of tissue that can affect any bony joint in the body. The hip joint is the most common location for ON and should always be properly evaluated, utilizing radiographic screening and MRI scanning, when ON is initially diagnosed in another body part. The earlier a diagnosis of ON is made, the better the opportunity to save the hip joint without surgical intervention or with minimally invasive surgical techniques.

After a diagnosis of ON is made, the size, extent, and location of the lesion and the classification stages are considered to develop an optimal plan of care. The presence or absence of symptoms is important in this process. The goals of treatment involve attempting to preserve the biological hip joint for as long as possible and consideration of a patient’s lifestyle and quality of life issues. To date, the 2 main therapeutic options for management of hip ON include joint-preserving procedures and THA. Patient education about potential risk factors and development of ON is essential to prevent the condition and/or to potentially prevent or halt progression of early-stage disease to later-stage disease.  

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Acknowledgement

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How to Cite this Article

References

Connections

Every activity of the living organism is connected with a separate part of the body whence it arises. Therefore, an activity is necessarily damaged when the part which produces it is affected.

— Galen of Pergamon, 130 AD-210 AD, prominent Greek physician, surgeon, and philosopher in the Roman Empire
Prolonged Survival in a Patient with Idiopathic Pulmonary Fibrosis Receiving Acupuncture and DHEA-Promoting Herbs with Conventional Management: A Case Report

Paul Kalnins, ND, MSOM; Mikael Brucker, ND, MAC; Donald Spears, ND, MSOM

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a common form of interstitial lung disease. The lung interstitium is defined as the supportive connective tissue in the parenchyma of the lung between the alveolar epithelium and the pulmonary capillary endothelium. Interstitial lung diseases affect the parenchymal area of the lung, impairing gas exchange, and fall under the functional category of restrictive lung diseases. In contrast, obstructive lung diseases manifest in the pulmonary airways, preventing pulmonary expiration.

IPF is a subset of a group of intestinal lung diseases called idiopathic interstitial pneumonia, with different courses, etiologies, and patterns of fibrosis. Liebow and Carrington created 5 histologic classifications of idiopathic interstitial pneumonia, with the most common being usual interstitial pneumonia (UIP), which accounts for between 47% and 64% of cases. Complicating matters, some medical circles group different types of idiopathic interstitial pneumonia together as IPF. Discerning categories in medical literature can be difficult. For the purpose of this article, IPF will refer to the disease consistent with the UIP histologic pattern.

Patients with IPF are usually older than age 50 years, and two-thirds are diagnosed after age 60 years. Disease prevalence is about 15 per 100,000 people in the US. Risk factors include male sex and a history of smoking. A small percentage, less than 4%, experience a familial form of the condition.

IPF has been found to be caused by excessive fibrotic response to alveolar epithelial damage. The pathogenesis was previously believed to be because of inflammatory-induced tissue changes; this revision explains the lack of efficacy of anti-inflammatory drugs in treating IPF. Alveolar damage induces a signal cascade from epithelial type I pneumocytes to type II pneumocytes to fibroblasts in the adjacent interstitium. The fibroblasts transform to myofibroblasts and deposit collagen. In IPF, the fibrous deposition pathway is excessive. Apoptosis of fibroblastic cells are downregulated, collagen fibers accumulate, and the interstitium thickens and hardens. Alveoli thickening reduces contractility and diffusion of gases in the parenchyma, resulting in a restrictive lung disease.

Although the pathway is well understood, the etiology of the dysregulation of the fibrotic response is not, hence the idiopathic nature of the condition. One theory suggests that injury causes damage to type I epithelium and the basement membrane of alveoli, allowing migration of fibroblastic cells from adjacent tissue into epithelium. Another theory suggests that the disease is a normal response to some chronic stimulus irritating the pulmonary tissue.

Diagnosis requires all 3 of the following components: 1) pulmonary function study results indicating evidence of restrictive lung disease; 2) high-resolution computed tomography of the chest showing reticular bibasilar abnormalities with minimal ground-glass appearance, in a typical UIP pattern; and 3) exclusion of other known causes of interstitial lung disease such as asbestosis. If these clinical and radiographic parameters leave diagnostic uncertainty, a lung biopsy specimen consistent with the UIP histologic pattern is definitive; however, other diseases such as rheumatic disease, hypereosinophilia, and pulmonary Langerhans cell histiocytosis (histiocytosis X) can present with identical histologic patterns to IPF.

The prognosis of IPF is grim, with a mean life expectancy of 2 to 4 years. Conventional medicine treatment focuses on palliation and prevention of respiratory exacerbation. Supportive treatments include supplemental oxygen, respiratory rehabilitation,
and application for lung transplants, although most patients are rejected for transplant lists because of their older age. IPF is the second-most common disease indication for lung transplant. The survival rate 5 years after transplantation is only 40% to 50%.1 All patients with IPF are advised to receive the pneumococcal vaccine to prevent further respiratory compromise.

The course of the disease varies. Some patients follow a steady linear decline, some succumb to a rapid decline, and others experience points of acute exacerbation that launch them into rapid decline. Patients are advised to protect themselves from respiratory assaults such as upper respiratory tract infections, because an acute exacerbation could lead to death. The American Thoracic Society recommends monitoring pulmonary functional values every 3 to 6 months to assess for disease progression and prevent worsening of acute exacerbations.³

Because of the high morbidity and mortality of IPF compounded with the limited efficacy of conventional therapies, clinicians may consider alternative therapies that could increase quality of life and life expectancy.

**CASE PRESENTATION**

**Presenting Concerns**

A 55-year-old man presented to the pulmonology clinic in spring 2007 with a chronic dry cough and dyspnea on exertion. He had no diagnosis of any serious pulmonary condition. Minor respiratory complaints, including shortness of breath, dated to at least 2004. The organic cause of his complaints at that time was unknown. He initiated weekly acupuncture treatments in 2004, which he maintained consistently for 13 years. The acupuncture treatments focused on treating the Chinese medicine diagnosis of spleen dampness. After 1 year of weekly acupuncture, the patient noticed improvement in shortness of breath.

In 2001, 6 years before initially presenting to his pulmonologist, the patient was quite active, hiking up to 10 miles in a day, before the insidious onset of his respiratory weakness. At presentation in 2007, he was obese with a body mass index of 36.8 kg/m² and had the following diagnoses: Stage 1 hypertension, allergic rhinitis, gastric reflux, and depression that was well managed with a selective serotonin reuptake inhibitor. The patient reported no history of severe asthma affecting his sister but no other respiratory illnesses. The patient was employed as an economics professor at a local university. He was single without children and lived alone.

Pulse oximetry readings (in the pulmonologist’s office in April 2007) revealed an oxygen saturation of 95% at rest, whichDeprecated to 79% with a 6-minute walk test. Results of cardiovascular, thyroid, abdominal, genitourinary, and neurologic examinations were unremarkable. Extremities showed minor pitting edema without evidence of peripheral or central cyanosis. The pulmonologist’s auscultation revealed diffuse crackles on inspiration bilaterally halfway up from the bases without prolonged expiration.

Because progressive dyspnea on exertion has many organic causes, including many types of restrictive and obstructive lung diseases as well as autoimmune and rheumatic causes, the pulmonologist completed a thorough workup to rule out differential diagnoses. Spirometry completed in October 2007 confirmed severe restrictive lung disease revealing a predicted forced vital capacity (FVC) of 54% and a predicted diffusing capacity of the lungs for carbon monoxide of 46%, but with a forced expiratory volume during the first second of expiration (FEV₁)/FVC index of 78%. Flow loops showed no sign of obstructed airways.

The pulmonologist ordered measurement of creatinine kinase, antineutrophil cytoplasmic antibody, antinuclear antibody, anticyclic citrullinated peptide, and aldolase to assess for autoimmune activity, in addition to creatinine and serum urea nitrogen to measure kidney activity; the results from these tests were unremarkable. The complete blood cell count showed no signs of systemic infection. A normal echocardiogram ruled out compromised cardiac function.

A chest computed tomography scan confirmed structural degeneration consistent with restrictive lung tissue showing subpleural cysts, honeycombing, and traction bronchiectasis. Because different forms of interstitial lung diseases have different prognostic forecasts, the pulmonologist completed a biopsy in September 2007. The biopsy specimen revealed a UIP histologic pattern, confirming a diagnosis of IPF. The invasive biopsy procedure was undertaken because of the severity of IPF and the necessity of ruling out other nonterminal or reversible conditions. Some clinicians, however, believe that a diagnosis of IPF can be made without biopsy because high-resolution computed tomography alone has a specificity of greater than 90%.³

**Therapeutic Intervention and Treatment**

The patient initiated weekly acupuncture therapy in 2004 focusing on spleen dampness. Chinese medicine diagnosis was made by assessing the pulse and the tongue and by palpating for tender Mu points on the body. In Chinese medicine, each organ has a corresponding Mu point, which is tender when overstressed. The patient’s tongue showed a thick white coating, his radial pulse expressed a slippery quality on palpation, and his Liver 13 acupuncture point (the Mu point for spleen) was tender. These signs and symptoms support a Chinese medicine diagnosis of spleen dampness. The diagnosis suggests that the spleen is not able to effectively process nutrition and fluid intake into the body, which was supported by the patient’s obese body habitus. Although the focus of treatment on spleen dampness remained unchanged, specific acupuncture point selection varied week to week depending on point tenderness and the acupuncturist’s discretion.

The pulmonologist placed the patient on supplementary oxygen therapy (4 L/min flow rate) for ambulation after first measuring his compromised ambulatory oxygen perfusion in April 2007. After the diagnosis of IPF in September 2007, the pulmonologist medicated him with azathioprine 50 mg, titrated up to 150 mg over 6 weeks; prednisone 60 mg, titrated down to 20 mg over 1 month; and N-acetylcysteine 600 mg 3 times daily, to boost production of antioxidants. This triple therapy was standard care at the time. The patient was not eligible for the lung transplant list because his body mass index was greater than 30 kg/m².
The pulmonologist weaned the patient off his prednisone regimen in April 2010 because of a change in the American Thoracic Society’s guidelines. Comprehensive data and recommendations from the Society revealed that corticosteroids and other immunosuppressive medications did not change outcomes; in fact, they may have contributed to morbidity and mortality for patients with UIP. In September 2012, the pulmonologist discontinued azathioprine therapy after the patient experienced a psychiatric breakdown.

In March 2016, the patient initiated naturopathic adjunctive care. The naturopathic physician prescribed botanical tinctures and adjusted them every few months to meet the patient’s evolving needs. The first formula was prescribed to stimulate production of dehydroepiandrosterone (DHEA). It was dosed in equal parts of Panax ginseng, Rhodiola rosea, Schisandra chinensis, Dioscorea villosa, Glycyrrhiza glabra, and Epimedium grandiflorum. He was instructed to take 15 drops in water 3 times a day.

**Follow-up and Outcomes**

The patient’s pulmonary radiographic and functional values were monitored every 3 to 6 months under the care of his pulmonologist. Biannual FVC measures were recorded (Appendix A, available at www.thepermanentejournal.org/files/2019/18-074-App-A.pdf). Pulmonary measures, including pulse oximetry, pulmonary function, and radiographic tissue changes, were assessed. The FVC value improved from 38% predicted at the time of IPP diagnosis in 2007 to 59% in October 2011 and steadily declined to a low of 41% in 2014. After 2014, FVC values were stable at around 40%.

In April 2010, the patient experienced an acute psychiatric breakdown involving multiple suicide attempts, and he was hospitalized and advised to take a leave of absence from work. During this period, he lost 18 kg (40 lb), reducing his risk of complications from obesity but placing him in danger of becoming cachexic. He lost any future possibility of being placed on a lung transplant list. His Chinese medicine diagnosis also shifted from spleen dampness to lung qi deficiency. Signs and symptoms that supported the new diagnosis were as follows: His body habitus was no longer obese; Lung Point 1, the Mu point for the lung, was tender; his radial pulse was less slippery and weaker on the distal right position; and his tongue no longer had a thick white coating.

<table>
<thead>
<tr>
<th>Table 1. Timeline of the case</th>
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**Notes:**
- BMI = body mass index; CT = computed tomography; CXR = chest radiograph; DHEA = dehydroepiandrosterone; DLCO = diffusing capacity of the lungs for carbon monoxide; FVC = functional volume capacity; URI = urinary tract infection.
In July 2014, the patient experienced an upper respiratory tract infection, which caused respiratory distress, tachypnea, and hypoxemia. This type of acute exacerbation could have induced a rapid decline; fortunately, the patient had discontinued the immunomodulation medication azathioprine 2 years earlier, and he was able to persevere, although his pulmonary function did not return to preexacerbation levels. After this exacerbation, the ambulatory oxygen rate was increased and the supplementary oxygen was expanded to support the patient at rest, with flow rates of 10 L/min and 4 L/min, respectively.

In March 2016, the patient began regularly seeing a naturopathic physician for botanical support. The prescribed herbal tinctures largely focused on the secretion of adrenal steroids from the adrenal cortex. The patient reported that he felt the tincture increased the efficacy of his acupuncture treatments regarding more ease with breathing.

In 2017, the patient’s pulmonary metrics were similar to his 2014 values. Although he experienced a gradual increase in symptoms, his vital signs on September 5, 2017, did not suggest hemodynamic compromise: Heart rate of 90 beats/min, blood pressure of 106/70 mmHg, and respiratory rate of 14/min. His pulmonary metrics reflected a slight but steady decline from those at the time of diagnosis. His resting pulse oximetry reading had declined from 91% to 84%, and his FVC had declined from 54% to 45%. He compensated by increasing supplementary oxygen to 8 L/min at rest and 15 L/min ambulatory. He was able to attend to his tasks of daily living and self-report to his acupuncture, naturopathic, and conventional medical appointments.

Shortly after a missed appointment—the first in several years—and unanswered telephone calls, the patient was found deceased at his home on February 27, 2018. Our patient survived 10 years after diagnosis of IPF. A timeline of his case is shown in Table 1.

Patient Perspective
The patient provided his perspective as follows: “In 2004, I was looking for further support for my respiratory condition, and my massage therapist recommended that I try acupuncture. I was told that my life expectancy was 3 to 5 years and that Western medicine did not have further treatments that could change that. I began weekly acupuncture treatments and feel that they have held off the slow decline that accompanies pulmonary fibrosis. A couple years ago, I switched to 1 acupuncture treatment every 2 weeks and noticed that I lost pulmonary function that I have not been able to get back. Since that time, I have had weekly acupuncture and have incorporated naturopathic medicine as well. I would tell anyone with pulmonary fibrosis that they should seek additional alternative medicine for pulmonary fibrosis. I attribute my current life expectancy to the support it has brought me.” (11/27/2017).

DISCUSSION
The prognosis of pulmonary fibrosis is grim. From 20% to 40% of patients survive only 5 years. Clinicians have few to no resources at their disposal that have proved effective for IPF. We chose the pulmonologist’s diagnosis of IPF in 2007 as the date of origin of the disease. One may be tempted to trace the origin of the patient’s condition further back to the dyspnea he began to experience in 2004, for which he initiated acupuncture. Because of a lack of conventional medical records from 2004, linking his dyspnea at that time to IPF would be speculative.

Our patient nevertheless beat the odds by surviving at least 10 years with IPF, which should pique clinicians’ curiosity to investigate his unique treatment management.

The triple therapy of N-acetylcysteine, azathioprine, and prednisone that the pulmonologist prescribed in 2007 was the standard of care at the time. Since that time, the medical community has moved away from the inflammatory pathogenesis of IPF to a fibrotic deposition hypothesis. The triple therapy has been shown to increase morbidity and mortality compared with placebo in at least 1 study. Since 2015, results of research surrounding nintedanib, a tyrosine kinase receptor blocker that prevents fibrogenic growth factors, have been promising. One study showed this medication halves the rate of decline of FVC compared with placebo. The therapy, researched only in patients at the mild or moderate stage of IPF, was not indicated for this patient.

Two treatment modalities for IPF that the patient used show promise for future research: Glycyrrhiza glabra (licorice root) and acupuncture. The medical literature has shown an indirect relationship between IPF and licorice root. Licorice has been shown to increase salivary levels of the parent adrenal steroid DHEA, and DHEA has been shown to be decreased in patients with IPF compared with control. In vitro, DHEA has also been shown to decrease both TGF-β1—a signaler for collagen production in IPF pathogenesis—and caspase-9, an intrinsic pathway signaler for fibroblast apoptosis. On the basis of these findings, a conceptual model worthy of further research is that DHEA modulates pulmonary fibrotic deposition, which is a process not well regulated in IPF.

A review of medical literature also revealed some study findings associating acupuncture with treatment of fibrotic tissue changes. One study showed reduced levels of serum markers for fibrotic deposition in rats with hepatic fibrosis compared with control. Another murine study corroborated the reduction in serum markers in acupuncture-treated rats with induced hepatic fibrosis compared with control. The study corroborated the serum markers with tissue biopsy confirming the results; however, it should be noted that the group in the second study was also treated with curcumin extract. Because the underlying mechanism causing the abnormal fibrotic tissue remodeling in IPF currently eludes biomedicine, the medical literature can at best extrapolate from other fibrotic conditions the mechanism by which acupuncture regulates fibrotic remodeling in IPF.
The medical literature already contains other case studies in which patients with IPF experience reduced symptoms and improved pulmonary function with regular acupuncture therapy. Clinicians may consider referring patients with IPF for adjunctive acupuncture and/or herbal therapy on the basis of the merits of this case and the other studies cited; however, larger clinical studies should be established to further test the efficacy of these therapies for treating IPF.

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

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How to Cite this Article

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Needles
The results in Japan which I will relate surpass even miracles.
For chronic pains of the head, for obstruction of the liver and spleen, and also for pleurisy, they bore through [the flesh] with a stylus made of silver or bronze.
— Jacobus Bontius (Jacob de Bondt), 1592-1631, Dutch physician and pioneer of tropical medicine
Bodie State Historic Park, in Bridgeport, CA, is located about 60 miles north of Mammoth Lakes. Visitors are transported back in time to the late 1800s in one of the best-preserved gold-mining ghost towns, and can see how people lived and struggled in those days. It is also eerie to envision how abruptly the town was abandoned. Many structures look practically as intact as the day their occupants left.

Dr Mallouk is a Nephrologist for the Southern California Permanente Medical Group. He very much enjoys exploring and photographing the great outdoors. More of his photographs can be seen in previous issues of *The Permanente Journal*. 
Long-Term Tumor-Free Survival in a Patient with Stage IV Epithelial Ovarian Cancer Undergoing High-Dose Chemotherapy and Viscum album Extract Treatment: A Case Report

Paul G Werthmann, MD; Robert Kempenich, MD; Gunver S Kienle, MD

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ABSTRACT

Introduction: Epithelial ovarian cancer (EOC) has a poor prognosis in advanced stages. High-dose chemotherapy (HDC) was pursued in the 1990s but was not found to improve survival of patients with EOC in larger studies. Many patients with cancer use Viscum album extracts (VAE). Also called European mistletoe, Viscum album can lead to improved quality of life and reduced chemotherapy side effects and may have synergistic cytotoxic and proliferation-inhibiting effects when used together with chemotherapy.

Case Presentation: A high-grade serous epithelial ovarian carcinoma with peritoneal, adrenal, and hepatic metastases (FIGO Stage IV) was diagnosed in a 50-year-old premenopausal woman. Tumor and metastases were surgically removed in cytoreductive surgery, and the patient received adjuvant chemotherapy, without experiencing side effects from treatment. After a second-look surgery revealed lymph node metastases, HDC and autologous hematopoietic stem cell transplantation were performed. Additionally, the patient opted for treatment with VAE, which she continuously received. The patient remained tumor-free in follow-up examinations and has enjoyed good health for 20 years after initial diagnosis.

Discussion: Treatment with VAE in this case might have contributed to the reduction of side effects from HDC and may have acted synergistically with HDC in tumor control. Cases of VAE in EOC should be carefully documented and reported to further illustrate the influence of VAE on this cancer presentation.

INTRODUCTION

High-grade serous carcinoma is presumed to originate from the fallopian tube and is part of the group of epithelial ovarian cancers (EOCs) that share many similarities regarding behavior and clinical course.1 EOCs have a fair prognosis in early stages but a poor prognosis in advanced stages, with a 5-year survival rate of 92% and 27%, respectively. Most EOCs are diagnosed at an advanced stage.2 Risk factors include a family history of gynecologic cancers, especially when associated with a BRCA gene mutation, which is a positive prognostic factor. Lower cancer stage, young age, low-grade and nonserous histology of the tumor, and patient’s un restricted performance status are further predictors of a more favorable outcome.2,3 Advanced EOC is treated with surgical cytoreduction and adjuvant chemotherapy. Combination therapy of platinum- and taxane-based regimens show the best results regarding survival.4 High-dose chemotherapy (HDC) with stem cell transplantation was developed in the 1980s to overcome drug resistance and prevent recurrence,5 but it did not prove to be effective in EOC regarding overall survival.6

Viscum album extracts (VAE) are made from European mistletoe (Viscum album L), a hemiparasitic shrub growing on different host trees (eg, apple, pine, elm, oak). Several commercial VAE preparations are used as supportive therapy in patients with cancer. They are administered parenterally, usually subcutaneously, in an increasing, individually adapted dose.7 VAE contain a variety of active ingredients; the lectins, in particular, have strong cytotoxic and apoptogenic effects and show synergistic effects with radiotherapy and chemotherapy. Downregulation of a variety of cancer genes involved in tumor progression has been shown, as well as a reduction of cell migration, interference with tumor angiogenesis, and selective cyclooxygenase-2 inhibition.8–10 With its compounds, VAE show immune-modulating effects and reduce tumor-induced immunosuppression.11,12 Clinical trials have shown an improved quality of life of patients with cancer13,14 and a promising effect on survival,13,15 whereas tumor remissions have been reported only in small trials and case reports, usually after high-dose and local VAE application.16–22 Side effects include frequent dose-dependent local skin reactions and flulike symptoms and occasional pseudoallergic reactions, but otherwise VAE therapy appears safe, even at higher doses.23

To our knowledge, no data on the combination of VAE and HDC have been published. We herein report a case involving this combination treatment.

CASE PRESENTATION

Presenting Concerns

A 50-year-old premenopausal white woman received a diagnosis of EOC with peritoneal, adrenal, and hepatic metastases (FIGO International Federation Gynecology and Obstetrics Stage IV). She was of healthy weight; enjoyed physical activities, especially hiking, in her spare time; had had 2 pregnancies and 2 births; breastfed each child for several months; and did not use contraceptives. Several relatives of the patient had gynecologic and other cancers: Breast cancer in 2 sisters and a cousin; probable ovarian cancer in her mother and a maternal

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Long-Term Tumor-Free Survival in a Patient with Stage IV Epithelial Ovarian Cancer Undergoing High-Dose Chemotherapy and Viscum album Extract Treatment: A Case Report

Therapeutic Intervention and Treatment

After diagnosis, the patient underwent bilateral ovariectomy and adnexectomy, hysterectomy, omentectomy, cholecystectomy, resection of carcinomatous nodes, metastasectomy of liver metastases (segments VI–VII), and resection of the right suprarenal gland. In pathologic investigation, a high-grade serous carcinoma was diagnosed; molecular testing was negative for BRCA-1 and BRCA-2 mutations. After surgery, she was treated with 6 cycles of carboplatin and cyclophosphamide. After termination of chemotherapy, a computed tomography scan showed suspicious-appearing lymph nodes in the pancreaticocolic region.

In a second-look surgery, the mesenteric lymph nodes were excised, after which they were histologically diagnosed as lymph node metastases from the EOC. Chemotherapy was changed to high-dose carboplatin and paclitaxel. The precise dosage could not be verified but we assumed it to be similar to regimens described by Sabatier et al. The patient subsequently underwent autologous hematopoietic stem cell transplantation.

After the initial diagnosis, the patient went to a physician (RK) specializing in oncology and with additional training in anthroposophic medicine and was treated with subcutaneous VAE in slowly increasing dosages (Table 1). Initially, fermented aqueous VAE from pine tree hosts was used (containing 0.75 ng/mg mistletoe lectin and 0.35 μg/mg viscotoxin). After termination of chemotherapy, VAE from apple tree hosts was used (containing 39.5 ng/mg mistletoe lectin and 1.4 μg/mg viscotoxin).

Table 1. Timeline of the case of a 50-year-old patient with epithelial ovarian cancer

<table>
<thead>
<tr>
<th>Time</th>
<th>Intervention/Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial diagnosis</td>
<td>Surgical removal of tumor and metastases</td>
</tr>
<tr>
<td>Phase 1</td>
<td>6x carboplatin + cyclophosphamide; VAE pini 1 mg - 20 mg subcutaneous 3/wk</td>
</tr>
<tr>
<td>Month 8+</td>
<td>Second-look surgery with removal of positive nodes and splenectomy</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Month 9 - 13 High-dose carboplatin + paclitaxel; VAE pini 1 mg - 20 mg, subcutaneous 3/wk</td>
</tr>
<tr>
<td>Month 13</td>
<td>Autologous hematopoietic stem cell transplantation</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Month 13 - year 3 VAE mali 20 mg, subcutaneous 3/wk</td>
</tr>
<tr>
<td>Year 3 - present</td>
<td>VAE mali 20 mg, subcutaneous 3/wk, with treatment breaks: 1 m out of 3</td>
</tr>
</tbody>
</table>

*Patient has been tumor-free since the surgery in month 8.
VAE mali = Viscum album extract from host apple tree; VAE pini = Viscum album extract from host pine tree.

The patient reported that the treatment with chemotherapy—even the HDC—was well tolerated, and apart from short, self-limiting periods of nausea, she showed no adverse effects. In regular follow-up examinations, no signs of recurrence or other tumor appearance have been detected. As of this writing, the patient has been tumor-free for 20 years and is in good health and enjoying good quality of life. This case report was prepared following the CARE Guidelines.

Follow-up and Outcomes

The patient reported that the treatment with chemotherapy—even the HDC—was well tolerated, and apart from short, self-limiting periods of nausea, she showed no adverse effects. In regular follow-up examinations, no signs of recurrence or other tumor appearance have been detected. As of this writing, the patient has been tumor-free for 20 years and is in good health and enjoying good quality of life. This case report was prepared following the CARE Guidelines.

DISCUSSION

We describe a woman with advanced and metastatic high-grade serous carcinoma who was treated with surgery, HDC, and VAE and reported no serious side effects from cytotoxic treatment and has had an extraordinarily long-term tumor-free survival in good health and without any restrictions. Because prognosis in advanced EOC is poor, we presume that VAE treatment contributed to this positive outcome.

However, other factors may have played a role in the course of our patient. Long-term survival in patients with advanced EOC stages has been described, but characteristics leading to long-term survival in patients with advanced tumor stage have not been conclusively detected until now. Furthermore, HDC might have positively affected the course of our patient. Although HDC could not be proved to influence survival and is therefore not generally recommended, it may have some beneficial effect in younger patients (aged < 50 years) and in carriers of BRCA mutations.

In the case presented here, the patient, aged 50 years at diagnosis, had negative prognostic characteristics such as the advanced tumor stage with metastases in the liver, renal gland, and peritoneum as well as the histologic subtype of a high-grade serous carcinoma. Nonetheless, the tumor-free survival time of our patient is extraordinarily long (20 years, still ongoing and with good health as of this writing). The patient tolerated chemotherapy well, even HDC.

Because antitumoral effects of VAE have been documented in a broad variety of preclinical studies, and because prolonged survival of patients with other types of cancer as well as reduced chemotherapy side effects have been reported with use of VAE, we presume that the adjunct VAE treatment and the anthroposophic treatment setting may have contributed to the favorable outcome.
Our case adds to preliminary positive results of 2 small randomized and 2 non-randomized VAE trials in the setting of EOC. Together, these results warrant the conduct of rigorous, further investigations of the influence of VAE treatment on tumor behavior, survival, and quality of life in patients with EOC.

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

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Author Contributions
Paul G Werthmann, MD, contributed to case report design, collected and provided data, was the principal author of the paper, and is the guarantor of the paper and all data. Robert Kempenich, MD, contributed to case report design and supervised the report and the publication process.

How to Cite this Article

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Image Diagnosis: Thoracic Epidural Hematoma from a Fall Requiring Emergent Decompressive Laminectomy and Hematoma Evacuation

Omar Viswanath, MD1,2; Cyrus Yazdi, MD1,2

Case Presentation
A 40-year-old man with a history of morbid obesity, posttraumatic stress disorder, and opioid addiction was admitted with progressive back and leg pain after falling while getting out of the shower 3 days earlier. He initially presented to a community hospital, where a lumbar computed tomography scan came back negative. He was subsequently sent home. His pain continued to progress until he was unable to walk, at which point he presented to a satellite Emergency Department of a large tertiary hospital. Given his morbid obesity, the patient was transferred to the main hospital, where he was admitted and underwent a lumbar magnetic resonance imaging scan under general anesthesia that showed multilevel spondylosis without central canal or neuroforaminal stenosis.

The initial physical examination was notable for thoracic midline and paraspinous tenderness, most predominantly localized in the T6 to T8 region, along with 4/5 diffuse left lower extremity (LLE) weakness, including knee and thigh flexion/extension, dorsiflexion, and plantarflexion, compared with the right lower extremity. There was decreased sensation to light touch throughout the LLE. Reflexes at the patellar tendon (L4) and Achilles tendon (S1) were 2+ on the right but 0 on the left. The Neurosurgery Department was consulted, and their recommendation was to obtain a cervical and thoracic magnetic resonance image. Given the patient’s size coupled with his anxiety, he required general anesthesia to obtain this imaging. The patient’s scan was ultimately delayed until the following morning because multiple traumas and emergency surgeries occurred that night.

The thoracic magnetic resonance image revealed an epidural hematoma at T6–T10 with cord compression (Figure 1). The patient underwent an emergent decompressive T6–T10 laminectomy and evacuation of the epidural hematoma. He was transported to the Neurointensive Care Unit and intubated. The next day he was extubated and started on a hydromorphone patient-controlled analgesia for his postoperative pain. In the acute postoperative period, our patient began to regain movement in his LLE but continued to have weakness. He was discharged on postoperative day 7 to an acute rehabilitation facility.

Teaching Points
- Even though the lumbar spinal nerves innervate the lower extremities, and the musculoskeletal and neurologic physical examination of the lower extremities may be largely normal, in our case, practitioners must be cognizant that there could be cord compression in a more superior location, including the thoracic spine. In addition, patients may have thoracic midline and paraspinal tenderness to palpation on physical examination.
- Our initial physical examination findings, including thoracic midline and paraspinal tenderness, 4/5 diffuse LLE weakness, and areflexia at the patellar tendon (L4) and Achilles tendon (S1) on the left, may have been underappreciated focal neurologic findings that should have supported the need for further imaging.
- The history of present illness always provides clues. Even though our patient was morbidly obese, he had been able to move around with ease and complete activities of daily living independently; in the days after the fall he was no longer able to do so. Such a precipitous decline in physical function is a crucial clue.

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

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ECG Diagnosis: Ibutilide-induced Torsade de Pointes

Daphne D Le¹; Joel T Levis, MD, PhD, FACEP, FAAEM²,³,⁴; Nelya Lugovskaya⁵; David R Vinson, MD⁶,⁷,⁸,⁹

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INTRODUCTION

Ibutilide is recommended by professional society guidelines for the cardioversion of atrial fibrillation and flutter.¹,² Its rapid effect and minimal impact on hemodynamics make it well suited for use in the Emergency Department (ED).³ Ibutilide, however, prolongs the corrected QT (QTc) interval and increases risk for ventricular tachycardia (VT).⁴-⁶ The risk of VT can be greatly mitigated by careful selection of low-risk patients, the optimal dose of prophylactic magnesium sulfate, and at least 4 hours of postibutilide electrocardiographic monitoring.³ This case illustrates the dangers of overlooking ibutilide contraindications and provides practical lessons in ibutilide use and management of ibutilide-induced VT.

CASE PRESENTATION

A 61-year-old man with a medical history of hypertension, type 2 diabetes mellitus, paroxysmal atrial fibrillation, and a recent community-acquired pneumonia, presented to the ED complaining of several hours of a rapid, irregular heart rate. He denied chest pain and shortness of breath. His initial vital signs were: Temperature, 37.1°C; systolic blood pressure, 107 mmHg; pulse, 139 beats/min; respiration rate, 16 breaths/min; and oxygen saturation, 95% on room air. His mental status and lung examination were normal, and his cardiovascular examination revealed a rapid, irregularly irregular pulse without murmurs. The initial 12-lead electrocardiogram (ECG; Figure 1) demonstrated atrial fibrillation with a ventricular rate of 118 beats/min, and a prolonged QTc interval of 488 msec (normal range 360-440 msec). He had a history of minimally prolonged QTc interval, measured, for example, at 452 msec while in sinus bradycardia 7 years earlier. See Figure 2 for the endpoints of the QT interval. We used Bazett’s formula to correct the QT interval for heart rate: QTc = Q - R / √R. His outpatient medications at the time of presentation included the following: Atenolol, warfarin, amlodipine, lisinopril-hydrochlorothiazide, glipizide, terbinafine, atorvastatin, allopurinol, and a 7-day course of cefpodoxime and doxycycline. None of these are known to directly prolong the QTc interval.

The patient received 3 serial 5-mg bolus injections of intravenous metoprolol for ventricular rate control, resulting in a ventricular rate of 85 beats/min. During the reduction in heart rate, he underwent another 12-lead ECG (not shown), which revealed a ventricular rate of 95 beats/min and a QTc interval of 488 msec. Laboratory tests were significant for a serum potassium of 3.1 mEq/L (normal range 3.5-5.3 mEq/L), a serum magnesium of 1.8 mEq/L (normal range 1.6-2.3 mEq/L), and an international normalized ratio of 1.2 (therapeutic target 2.0-3.0). The patient received 1 g intravenous magnesium sulfate over 30 minutes, followed by 2 intravenous infusions of ibutilide (10 mg each, separated by 30 minutes) for pharmacologic conversion to sinus rhythm. Shortly after completion of the ibutilide infusions, his atrial fibrillation resolved, and he developed ventricular bigeminy with intermittent episodes of sustained polymorphic VT (Figure 3). The patient remained hemodynamically stable throughout these VT episodes (systolic blood pressure approximately 135 mmHg). Intravenous magnesium sulfate (1 g over 30 minutes) was administered without complication.

Figure 1. 12-lead electrocardiogram from a 61-year-old man with palpitations. Demonstrates atrial fibrillation with a ventricular response of 118 beats/min, and a prolonged QTc interval of 488 msec.

Figure 2. How to measure the QT interval on an electrocardiogram.

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Keywords: atrial fibrillation, atrial flutter, cardioversion, ECG diagnosis, ibutilide, polymorphic VT, prolonged QTc interval, torsade de pointes
amiodarone (150 mg) and magnesium sulfate (4 g) were then administered. His cardiac rhythm converted to sinus bradycardia with a prolonged QTc interval of 600 msec and inverted T waves (as a result of repolarization changes following pharmacologic cardioversion; Figure 1). The patient began oral potassium replacement in the ED and was admitted to the Intensive Care Unit overnight for close monitoring. He had no further episodes of ventricular dysrhythmia and was discharged the following day in sinus rhythm with a corrected serum potassium, a heart rate of 43 beats/min, and a QTc interval of 572 msec.

**DISCUSSION**

The ED management of the stable patient with primary nonvalvular paroxysmal atrial fibrillation or flutter and recent-onset symptoms may include attempts at pharmacologic or electrical cardioversion. The choice to pursue the restoration of sinus rhythm in the ED is influenced by many variables and is well suited for shared decision making. An ED rhythm-control strategy was a viable option for our patient, although the selection of ibutilide was not ideal because he had 2 notable contraindications: A prolonged QTc interval and hypokalemia. Both of these are known to increase the risk for polymorphic VT, which is a dangerous rhythm that can degenerate into ventricular fibrillation and cause cardiac arrest. Among pharmacologic agents for the cardioversion of recent-onset atrial flutter, however, ibutilide is unrivaled (eg, ibutilide had a 64% cardioversion rate at 90 minutes vs 22% for procainamide).

Polyomorphous VT is the most serious side effect of ibutilide. The multiple ventricular foci of polymorphic VT are evident in QRS complexes of varying amplitude, axis, and duration. When associated with acquired or congenital QTc interval prolongation, polymorphic VT is called torsade de pointes (TdP). This French term has 2 complementary meanings: 1) “twisting of points,” referring to the ribbon-like twisting of the rhythm around the ECG isoelectric line; and 2) “fringe of pointed tips,” another apt description of the ECG image (Figure 3). TdP is uncommonly captured on a 12-lead ECG because of the brevity and paroxysmal nature of the dysrhythmia and the gravity of the clinical situation.

Risk factors for drug-induced TdP include hypokalemia, female sex, drug-drug interactions, advancing age, genetic predisposition, hypomagnesemia, heart failure, bradycardia, and QTc interval prolongation. Numerous medications are known to prolong the QTc interval, including levofloxacin, erythromycin (and other macrolides), haloperidol, and methadone, as well as class III antiarrhythmics such as ibutilide. These medications induce TdP by inhibiting positive ion channels, making individuals with preexisting hypokalemia particularly susceptible to TdP. Because the QTc interval is generally more prolonged as the heart rate slows, polymorphic VT develops more commonly in bradycardic hearts, after ibutilide has resolved atrial fibrillation or flutter (as in our patient).

The most common and effective treatments for TdP include defibrillation and intravenous magnesium sulfate for unstable patients and magnesium sulfate alone for stable patients, regardless of baseline serum magnesium levels. Intravenous lidocaine (a Class Ib antiarrhythmic agent), which shortens the QTc interval, can also be useful. If TdP persists or recurs despite initial interventions, temporary overdrive pacing or intravenous isoproterenol can be used because these increase the heart rate and thereby shorten the QTc interval. Class Ia (eg, procainamide) and class III antiarrhythmics (eg, amiodarone, ibutilide, sotalol) should be avoided because they prolong the QTc interval and can aggravate TdP. Although amiodarone has been occasionally successful in the treatment of TdP, its use is discouraged given the unfavorable risk-benefit profile in this population and the availability of safer, more reliable TdP treatments. In addition to treatments aimed at terminating TdP, causative medications should be discontinued and electrolyte deficiencies corrected.

**CONCLUSION**

This case teaches us several important clinical lessons. First, ibutilide should be avoided in patients with hypokalemia or prolonged QTc interval. Defibrillation would have been a safer
choice than pharmacologic options for restoring sinus rhythm in this patient. Second, the 1-g dose of prophylactic magnesium that was administered as an adjunct to ibutilide was insufficient to either facilitate cardioversion or reduce the incidence of ibutilide-induced TdP. The dose of magnesium needed to enhance ibutilide effectiveness, even in patients with normal serum magnesium levels, is 2–4 g. The dose of magnesium required to minimize TdP is 5 g during the 1 hour preceding ibutilide administration and then 5 g during the 2 hours following the ibutilide infusion. 3,21 (Ibutilide is contraindicated in patients with low magnesium levels.) Third, amiodarone is not ideal for TdP treatment, as noted above. 19,20,24,25 When used properly, ibutilide can be an effective—and relatively safe—medication for the cardioversion of recent-onset atrial fibrillation and flutter.1

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

How to Cite this Article


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Electrical Activity

That [electrical] activity first reveals itself in the region of the sin-auricular node … has been shown … beyond question. It spreads from this node in every direction, progressing to all the margins of the musculature.

This photograph is part of a series taken in remembrance of the worst wildfire in California history. These images were taken in the community around the Santa Rosa Medical Center.

Dr. Chen is Medical Director and a Pathologist at the Santa Rosa Medical Center in CA. More of Dr. Chen’s photographs can be seen on the cover and page 69 in this issue of The Permanente Journal.
Effect and Durability of an In-depth Training Course on Physician Communication Skills

James T Hardee, MD; Thomas F Rehring, MD; Joseph E Cassara, MD; Karl Weiss, MBA; Nicholas Perrine, PhD

ABSTRACT

Introduction: Effective clinical communication skills are integral to a successful and therapeutic clinician-patient relationship and are associated with improvement in adherence, outcomes, and lower medicolegal risk. However, in stark contrast to other clinical and cognitive skills, practicing physicians generally receive little ongoing training or assessment of individual performance in communication.

Objectives: To assess the effect of an in-depth physician communication course on patients’ perception of clinician skill in communication.

Methods: We analyzed the effect of a 3-day dedicated course on clinical communication skills among 65 clinicians assessed by a randomized patient survey.

Results: Patients were significantly more satisfied with their physician on 6 specific communication skills after the physician received the Communication Skills Intensive training. The effect persisted at 12 months’ follow-up. In addition to the improved patient satisfaction scores, attendees stated that they learned many practical communication skills and valued the course.

Conclusion: Health systems looking to improve patient experiences, demonstrate empathy, and invest in the end), such as the Four Habits (invest in the beginning, elicit the patient's perspective, demonstrating empathy, active listening, delivering an appropriately detailed explanation, and shared decision making. These skills are key components of many commonly used communication models such as the Four Habits (invest in the beginning, elicit the patient’s perspective, demonstrate empathy, and invest in the end), the E4 model (engaging, empathizing, education, and enlisting), ALERT (Always: Listen carefully, Explain understandably, Respect what the patient says, and manage Time perception), and ILS (Invite, Listen, Summarize).

Although attention to clinical communication is now common in many medical school and residency curricula, there remains a need for practicing clinicians to refresh and refine their communication skills. The consequences of workload compression and reduced visit times can threaten the effectiveness of clinician communication. Modern practices are faced with time constraints, increasing patient demands, high medical complexity, financial difficulties, and electronic medical record charting. A number of organizations have sought to address and reinforce communication skills for practicing physicians, including university training programs, medical groups, and independent companies. The programs offered run the gamut from online modules and videos, to one-on-one coaching, brief lectures, half-day and full-day classes, and multiday intensive courses. Each of these requires resource allocation, not only for participating in the program itself but also indirect costs from taking clinicians out of the patient care environment for that time. The aim of this study was to assess the effect of an in-depth physician communication course on patients’ perception of clinician skill in communication.

METHODS

Course Description and Study Sample

Kaiser Permanente Colorado offers a biannual Communication Skills Intensive (CSI) course for clinicians wishing to improve their communication by providing them with the opportunity to learn and practice new skills outside the examination room. The Kaiser Permanente Colorado CSI course consists of 3 full days of training among a group of 16 to 20 participants. The course was designed and implemented following a similar program created by Stein using content-based lectures, small-group skills practice with care actors, group feedback, and self-reflection. Participation in the CSI is completely voluntary; although most participants self-selected to participate, a lesser number were encouraged to attend. Absolutely no participants were forced or coerced to join the program, and attendance was never made a condition of employment. The mechanism by which a particular attendee arrived at the course was confidential and not made known to faculty or other participants. The participant-to-faculty ratio was 2:1, which allowed for a high degree of coaching and facilitation.

Participants included for this assessment were 75 clinicians who attended the course between 2010 and 2016. Ten of those clinicians were also in leadership positions and were removed from the analysis because their primary duty was as a leader, not as a clinician, and they therefore received unique training on “Staff
Coaching” and “Leadership Conversations.” Thus, 65 participants who attended the CSI training between 2010 and 2016 were included in this analysis. Three (5%) of the 65 clinicians who attended CSI training were physician assistants, and the remaining 62 (95%) were physicians. Forty-four (68%) of the clinicians were from primary care departments (Internal Medicine, Family Medicine, Pediatrics). The remaining 21 clinicians (32%) were medical specialists or surgeons (eg, emergency medicine, gynecology, psychiatry). Twenty-nine (45%) of the clinicians attending the CSI course were men. Years of practicing medicine at Kaiser Permanente ranged from 0 to 27 years, with a mean of 6.27 years and median of 3 years.

**Art of Medicine/Patient Feedback of Clinician Communication**

Patient ratings of clinicians’ communication skills were assessed using a commercial standardized survey (Art of Medicine [AoM], HealthCare Research, Denver, CO). The AoM patient survey collects a minimum of 75 completed surveys per clinician per year. Patients with a recent clinician encounter are randomly selected to complete a brief survey about the clinician on several aspects of their communication (eg, listening, explaining, treating with courtesy/respect, understanding the patient’s concerns, managing fear and anxiety, and an overall interaction rating). Data collection for the AoM program is continuous. The 65 clinicians who completed the CSI course had AoM survey data for the year before and the year after the clinician’s attendance at CSI.

**Data Analysis**

The effectiveness of the CSI training was assessed using paired-samples t-tests before and after the CSI training performance on the AoM patient survey program. Specifically, paired-samples t-tests compared patient ratings of a clinician’s communication effectiveness from the year before the CSI training against ratings from the year after CSI training. Additionally, the annualized pre- and post-CSI training data were aggregated by month across all 65 clinicians who attended CSI training, to compare patterns in monthly performance for the 12 months leading up to and 12 months after training.

**RESULTS**

Six separate paired t-tests were performed comparing pre- and post-CSI training performance on key communication skill items from the AoM patient survey (Table 1). Results from those statistical tests suggest that patients were significantly more satisfied with their physicians on all 6 AoM communication skills questions after CSI training compared with their ratings before attending the CSI training. For example, the average patient rating of “Overall interaction” before training and after training was 73.8% and 77.0%, respectively (Figure 1).

![Figure 1. Patient ratings of overall physician interaction 12 months before and after Communication Skills Intensive (CSI) training.](image)

Whereas results from the paired-samples t-test suggest that patient ratings of clinician’s overall interaction was significantly higher after clinicians completed the communication skills training compared with before receiving training, the findings do not indicate the practical effect or clinical importance of the training. Dividing the mean change in overall interaction (3.23%) by the difference in standard deviation between pre- and posttraining (0.122) yields a Cohen $d$ effect size of 0.26. Although t-tests provide an indication of statistical importance (ie, is the change in patient ratings owing to the intervention or is it owing to random chance), the Cohen $d$ effect size quantifies the practical significance of the training. A Cohen $d$ effect size of 0.26 is somewhere between a small and medium effect size. One interpretation of this effect is that the mean patient rating of overall interaction among clinicians who completed training is better than 60% of clinicians before receiving training (ie, at least a 10-percentage point improvement in mean performance between the distribution of scores before and after training). More importantly, a patient’s satisfaction with his/her clinician

**Table 1. Pre- and post-Communication Skills Intensive (CSI) training performance on key communication skill items from Art of Medicine patient survey**

<table>
<thead>
<tr>
<th>Communication skill</th>
<th>Sample size (n)</th>
<th>Pre-CSI average (%)</th>
<th>Post-CSI average (%)</th>
<th>t statistic</th>
<th>p value</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall physician interaction</td>
<td>65</td>
<td>73.8</td>
<td>77.0</td>
<td>2.13</td>
<td>&lt; 0.05</td>
<td>0.1222</td>
</tr>
<tr>
<td>Courtesy/respect</td>
<td>65</td>
<td>79.6</td>
<td>83.4</td>
<td>3.86</td>
<td>&lt; 0.001</td>
<td>0.0806</td>
</tr>
<tr>
<td>Listening</td>
<td>65</td>
<td>74.9</td>
<td>79.1</td>
<td>3.29</td>
<td>&lt; 0.01</td>
<td>0.1028</td>
</tr>
<tr>
<td>Understanding</td>
<td>57</td>
<td>73.5</td>
<td>77.1</td>
<td>2.66</td>
<td>&lt; 0.05</td>
<td>0.1020</td>
</tr>
<tr>
<td>Explaining</td>
<td>65</td>
<td>73.5</td>
<td>77.4</td>
<td>2.97</td>
<td>&lt; 0.01</td>
<td>0.1054</td>
</tr>
<tr>
<td>Managing fear and anxiety</td>
<td>57</td>
<td>59.6</td>
<td>65.4</td>
<td>2.49</td>
<td>&lt; 0.05</td>
<td>0.1753</td>
</tr>
</tbody>
</table>

* Pre- and post-CSI averages represent percentage of patients providing a 5 (excellent) rating on a 1 to 5 scale (ie, top-box rating). SD = standard deviation.
is related to improved compliance and adherence with treatment plans.\textsuperscript{18} Specifically, patient compliance with and adherence to recommended treatment plans increase as patient satisfaction with a clinician increases. Therefore, training programs with even small effect sizes that demonstrate positive impact on patients’ ratings of their physicians could mean the difference, for example, between a patient taking medications as prescribed vs skipping days or discontinuing a medication once visible signs of disease disappear.

The mean performance of the 65 clinicians who completed the CSI course changed from a score of 73.8% before course completion to a postcourse completion score of 77%. This improvement in average performance after completing the communications course resulted in 5 additional clinicians averaging a patient rating greater than 74% a year after course completion (34 clinicians before vs 39 after; Figure 2.)

At the conclusion of each CSI course, attendees were asked to provide anonymous written evaluations pertaining to their experience and learnings. Comments were overwhelmingly positive in terms of practical learnings and perceived value of the program (see Sidebar: Feedback from Attendees of the Communications Skills Intensive Course).

**DISCUSSION**

A variety of virtual and in-person clinical communication training programs exist, but little is known about their short- or long-term effectiveness, specifically, when it comes to patient ratings of physicians. In 1999, Brown et al\textsuperscript{19} reported that clinician participation in a 2-day (10-hour) communication skills training program did not improve patient satisfaction ratings on the AoM survey. Although participants’ self-reported ratings of their communication skills increased, the mean AoM score actually improved more in the control group than in the participant group, leading the authors to postulate whether communication skill training programs needed to be longer and more intensive.

Perhaps taking the aforementioned suggestions to heart, Stein\textsuperscript{16} in 2007 published the results of a 10-year retrospective study looking at the outcomes of a multiday, residential CSI program. Similar to our program, Stein’s residential course required a substantial commitment of time and resources. Participants in both trainings completed prework reading, participated in didactic lectures and group discussion, and then practiced communication skills with highly trained improvisational care actors.\textsuperscript{20} Peer feedback and self-reflection were also key
components of both courses. Stein demonstrated a significant and sustained improvement in Member Patient Satisfaction scores after attendance at her program, concluding that the benefit extended to physicians, patients, and health care organizations.

Fallowfield et al.21 enrolled 160 UK oncologists into a 3-day communication skills training course (using structured feedback, videotape review, role-play with simulated patients, and interactive discussion). They demonstrated significantly improved use of open-ended questions and expressions of empathy but did not specifically monitor actual patient satisfaction. Building on the notion that cancer care physicians need especially good communication skills, Lenzi et al.22 enrolled Italian oncologists in a 3-day intensive workshop also focusing on lectures, small-group work, and role-play. Improvement was seen when the researchers compared before and after questionnaires on practitioners’ self-knowledge of communication skills and assessment of patients’ fears and concerns, but again patient satisfaction scores were not evaluated.22

In our study, patient evaluation of specific communication skills was universally improved as a result of the 3-day intensive communication skills course across a range of medical specialties. Our program was not limited to a single specialty communication focus (ie, oncologists only). Perhaps most importantly, the “overall” rating of the physician was statistically significantly higher. This effect was durable and found to persist up to 12 months after the course.

In reviewing the outcomes from these studies, one might wonder why the outcomes seem more robust with the passage of time. Certainly, there has been increased focus on the importance and value of excellent clinical communication skills.23 Medical schools and residency training programs now place a strong emphasis on clinical communication in their curricula, meaning that physicians are beginning their practices much more skilled in this area. In addition, patient satisfaction with their clinicians’ communication skills has become increasingly publicized, whether in a rigorous reporting format (Consumer Assessment of Healthcare Providers and Systems survey)24 or more informal Web sites such as third-party reviews and social commentary. Thus, clinicians’ awareness of this critical aspect of their practice has likely increased.

Figure 1 illustrates the statistically significant improvement in patient ratings among clinicians who completed the CSI course. Figure 2 portrays improvement in patient ratings in terms of individual clinician performance. Specifically, 5 additional clinicians exceeded the 74% patient rating threshold after participating in communications training. An examination of the lower-performing clinicians from Figure 2 suggests that 7 clinicians had an average performance below a 60% threshold before training compared with just 1 clinician performing below 60% after completing communications training. Clinical leaders should be encouraged by these findings that otherwise skilled physicians who might struggle with certain aspects of communicating with patients are able to improve that critical aspect of their medical practice. Generalizability of our results to other communication intensive courses would depend on many factors, including participant selection and engagement, course content and design, and faculty quality.

A final question pertaining to these and similarly published results is “So what?” Maybe it is not surprising that taking a group of professionals off-site and equipping them with practical communication skills leads to improved patient satisfaction scores. Perhaps the more important outcomes occur later, indirectly and beyond easily measurable parameters. That patients are statistically significantly more satisfied with their physician’s communication skills is admirable, but if this effort ultimately leads to improved adherence, better health outcomes, lower malpractice risk, stronger therapeutic alliances, reduced physician burnout, and health care cost savings, then the investment would seem to be more than worth it.

CONCLUSION

A 3-day concentrated educational effort to enhance clinician communication skills is an effective method of improving patients’ satisfaction scores with their physician. Patients were significantly more satisfied with clinicians on 6 specific communication skills after training compared with prior results. The effect was persistent at a mean of 12 months of follow-up. Health systems looking to improve patient-reported outcome measures should consider focused training, resources, and time for physicians to engage in an intensive communication skills course.

Disclosure Statement

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Effect and Durability of an In-depth Training Course on Physician Communication Skills


Uniting Tenderness with Steadiness

Hospital physicians and surgeons should minister to the sick … reflecting that the ease, the health, and the lives of those committed to their charge depend on their skill, attention, and fidelity. They should study … in their deportment, so to unite tenderness with steadiness, and condescension with authority, as to inspire the minds of the patients with gratitude, respect, and confidence.

— Thomas Percival, 1740-1804, English physician, health reformer, ethicist, and author
Is There a Lack of Support for Whole-Food, Plant-Based Diets in the Medical Community?

Maximilian Andreas Storz, MD

COMMENTARY

ABSTRACT
Since the early 2000s, plant-based nutrition has increased in popularity in the general population. Kaiser Permanente significantly contributes to this development by promoting plant-based diets and by continuously incorporating plant-based nutrition on the front lines with their dietary recommendations. Despite a continuously growing body of evidence and the meticulous work of renowned experts in this field worldwide, the latest findings in this area have not found their way into US national dietetic guidelines.

We must ask ourselves why this is the case, given the numerous advantages and health benefits of a whole-food, plant-based diet. What role do physicians play in this context? Is there potentially a lack of support for whole-food, plant-based diets and comprehensive lifestyle change programs in the medical community?

INTRODUCTION
A whole-food, plant-based diet (PBD) is a diet rich in vegetables, legumes, fruits, whole grains, nuts, and seeds. Meat, poultry, fish, dairy products, and processed foods are heavily restricted. PBDs have been associated with weight loss, a lower prevalence of hypertension and diabetes, and a reduced risk of heart disease. A recent meta-analysis found a significant protective effect of a vegan diet (where all animal products are excluded) in the incidence of total cancer. Moreover, studies suggest that a PBD may be beneficial in the treatment of several chronic diseases such as rheumatoid arthritis.

Kaiser Permanente has significantly promoted plant-based nutrition and has argued in favor of the large number of benefits of PBDs. The 2013 report by Tuso et al reviewing the benefits of PBDs proposed that physicians “should consider recommending a plant-based diet to all their patients.” They concluded that a change in Western culture’s mindset “from live to eat to eat to live” is vital to reversing the global obesity epidemic.

Although current evidence supports the health advantages of plant-based nutrition, implementing it into daily practice remains a challenge. Initiating a constructive dialogue with patients about this topic often resembles a balancing act requiring empathy and subtlety on the one hand and perseverance and clearly defined targets on the other. To facilitate this process, the 2016 report by Hever provides a 6-step guide to initiate and maintain a nutritional dialogue with patients. The author concluded that eating a PBD resembles a “win-win situation” for health care practitioners and patients alike. Plant-based nutrition is no longer a marginal phenomenon and is gradually being seen as a considerable alternative to strictly pharmaceutical therapies.

Worldwide renowned experts such as Dean Ornish, MD; Neal Barnard, MD; and Caldwell B Esselstyn Jr, MD, have provided valuable scientific evidence and meticulously advocate for plant-based nutrition, along with other comprehensive lifestyle changes, but their recommendations have not yet found their way into national guidelines. How can we explain why thorough counseling on whole-food, plant-based nutrition is currently not standard procedure in the treatment of cardiovascular and chronic diseases? Regarding the latest scientific findings and the numerous advantages and health benefits of these diets, we must ask ourselves why, precisely this is the case and what role physicians play in that context.

The crucial questions are: Is there potentially a lack of support for PBDs among medical professionals? Which factors impede the advance of comprehensive lifestyle change programs?

It is likely that some physicians would not officially admit recommending or adhering to a PBD to avoid negative or, in some cases, even pejorative comments from colleagues, researchers, and patients. According to Campbell, medical science is “deeply suspicious of everything claiming to be a panacea.” There also is still considerable insecurity about PBDs in the medical community. Unfortunately, this insecurity too often results in an unfounded rejection of PBDs. We will discuss 3 of the main factors contributing to this insecurity.

THE TIME FACTOR
Counseling patients on how to adopt a lifestyle change and how to successfully switch to a PBD requires time and attention to detail. Such a task may not be completed in a few minutes but often requires many hours and repetitive sessions. Simply advising a patient to consume more vegetables while avoiding unhealthy foods, such as processed red meats and refined sugars, is not the key to success. It is vital that patients understand and internalize what caused their disease and why. Only then may they be empowered to change their habits and unhealthy attitudes. However, physicians who see 30 or more patients a day simply lack the time to do this.

A 2017 study by Devries et al revealed that more than 50% of all cardiologists participating in their survey spent less than 3 minutes on discussing nutrition during an average patient appointment. Moreover, in the hospital setting schedules are rigorously timed. Consequently, even the most motivated and enthusiastic practitioner will encounter problems in finding the time for thoroughly counseling patients. The fact that health insurance companies usually do not reimburse for nutritional counseling further complicates this situation. To boost the popularity of PBDs among physicians and to increase...
the frequency of nutrition counseling, it is critical that a more attractive framework be created to allow physicians to spend more time on this important task. As long as many physicians are unable to witness the health benefits of PBDs because of a lack of time, the insecurity with this therapy will prevail.

THE TRAINING FACTOR

Many physicians possess insufficient knowledge about nutrition and seem to have an insufficient background to counsel patients. Devries et al.20 revealed a deficiency of nutrition education and practice among cardiovascular specialists: 90% of the cardiologists participating in their survey reported receiving only minimal or no nutrition education during fellowship training (33% and 57%, respectively). Additionally, nearly one-third did not recall receiving nutrition education at all during medical school. This deficient situation also has been outlined in 2010 by Adams et al.19

Adams et al.20 also found in their 2009 survey that US medical students overall received only 19.6 contact hours of nutrition instruction during their time at medical school. As measured by nutrition’s importance for cardiovascular health, this number already resembles a small amount of time, and it even declined compared with a survey by the same researchers in 2004.19 In another study in 2015, the authors affirmed their previous findings by concluding that “many US medical schools still fail to prepare future physicians for everyday nutrition challenges in clinical practice.”20

Weinsier et al.21 reported in 1988 that the number of medical students considering nutrition important for their career decreased by 15% during medical school. Reviewing these findings, we must conclude that a negative trend is taking place and that we are missing the chance to educate medical students in the health effects of PBDs at crucial points in their training. The percentage of vegetarians among medical students also seems to decline during medical school years. A study by Spencer et al.22 highlighted that freshman do not maintain their vegetarian diet during medical school despite an increase in medical education. On the basis of that, it seems that the perceived relevance of nutrition and nutrition counseling by US medical students declines during that period.23

A potential reason for this lack of knowledge might be that recent study findings have not yet found their way into medical textbooks and teaching resources. Too often, educational resources contain only one-sided information about PBDs. Potential benefits are rarely outlined in detail. Instead, generalized and abstract terms such as “protective” are used. As a corollary, students only develop vague ideas about the power of plant-based nutrition.

Nutritional education must be comprehensive and balanced. Students should be taught about both the health benefits and potential risks of a whole-food PBD. Potential deficiencies in macronutrients and micronutrients, such as calcium and iron, caused by following a poorly constructed PBD, must be addressed. It is also essential to enable students to differentiate between a healthy and an unhealthy PBD.24 Lastly, students should learn that certain patient groups (such as patients with kidney disease or thyroid disease, or patients with severe obesity) need close supervision for medical reasons when changing to a whole-food PBD.

It seems that some US medical schools have now embarked on rigorous curricular reforms to allow nutrition to “become a mainstream component of medical education.”25 The integration of lifestyle medicine, including nutrition, into modern medical education and interdisciplinary team-based learning opportunities is particularly worth mentioning here. The course “Food Matters for Doctors” from the University of Minnesota serves as a great example.26 Such interdisciplinary classes, which pair teaching about nutritional issues with hands-on experience preparing nutritious food, allow for a shift from abstract theoretical learning to solution-based, real-world experience. Instead of primarily memorizing enzymes in metabolic pathways, students are actively empowered to have practical and meaningful conversations about nutrition at the bedside.

Another player worth mentioning in this context is the American College of Lifestyle Medicine,27 which emphasizes the use of lifestyle interventions in the treatment of disease. Their educational resources and classes “specifically tailored for medical students”27 may also contribute to a tectonic shift in the current nutritional education of prospective physicians.

THE ECONOMIC FACTOR

Some studies associate PBDs with a reduction in "medication needs.”24,28,29 However, at least to some extent, patients not only expect physicians to listen to their history and complaints but also to treat them "properly" by prescribing medication. Modern serial medical dramas on television, hospital movies, and pharmaceutical advertisements suggest and insinuate that even the most complex disease can be easily cured by taking a single pill, further contributing to patient expectations toward physicians. For some people it is hard to understand that implementing a PBD, and hence adopting a lifestyle change, is necessary when potentially comparable benefits could be achieved by taking a medication.

Creating a well-balanced, nutrient-dense meal plan and avoiding highly processed products, such as refined white sugar and red meat, is undoubtedly more demanding than simply taking a pill once or twice a day. As a corollary, a physician who prefers to encourage lifestyle changes over rapidly prescribing medication might lose a certain amount of patients who, in turn, opt for the easiest achievable way to treat their disease. Hence, there is also a potential underlying economic motivation in why some physicians may not regularly counsel patients on PBDs. Talking about economic factors in this context is necessary because it is undeniable that financial interests play a role in the ongoing debate about plant-based nutrition. A shift from corporate-funded, industry-tailored recommendations to dietetic guidelines “beholden only to […] the patients they serve”20 will be necessary to realize changes.

CONCLUSION

To my knowledge, there is no substantiated data about the number of physicians recommending a PBD to their patients. Reviewing some of the recent studies, it is obvious that plant-based nutrition has not yet found its way into the standard treatment repertoire of many practitioners. Although the 3 factors of time, training, and economic interests discussed above represent only a few of the many variables influencing the current situation, they also constitute potential starting points to tackle this development.

By reducing physicians’ insecurity and skepticism toward plant-based nutrition,
more and more practitioners may be convinced to implement this cost-efficient yet highly effective treatment option in their daily clinical routine. It is vital to better educate the future generations of physicians—today's medical students—in this area. Online resources and modern technologies may play a key role here. The Physicians Committee for Responsible Medicine, a nonprofit organization founded by Neal Barnard, MD, provides a wide array of free online resources on their homepage. Their nutrition app “The Nutrition Guide for Clinicians” is particularly worth mentioning. Additional useful resources include the website “Nutrition Facts” by Michael Greger, MD, and “The Plantrician Project.”

Politicians, health care providers, and government administrations must create appropriate frameworks and conditions and provide a greater economic incentive to support motivated physicians in PBD counseling. Although this might involve considerable effort, time, and unpleasant dialogues with industry and capital interests, it will ultimately contribute to an improvement in public and environmental health. Plant-based nutrition might be the key to central issues of our time, such as the global obesity epidemic, exploding health care expenditures, and environmental destruction.

Because nutrition is inextricably connected to human health, physicians play a key role in further promoting and spreading the knowledge about PBDs. Interdisciplinary collaboration with nutrition educators and dieticians is necessary to reduce the insecurity toward PBDs in the medical community. As Benjamin Franklin is purported to have said, “an investment in knowledge pays the best interest.” Once physicians educate themselves further in plant-based nutrition, the medical community may start to appreciate this powerful tool and use it along with pharmacotherapy to provide better health treatment.

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COMMENTARY

Westernized Diet is the Most Ubiquitous Environmental Factor in Inflammatory Bowel Disease

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ABSTRACT

Inflammatory bowel disease (IBD), a collective term for Crohn disease and ulcerative colitis, is a polygenic disease thought to be triggered by environmental factors. A Western or westernized lifestyle may be a major driver of the growing incidence of IBD. IBD may represent dysregulated mucosal inflammation to gut microbiota. Despite many review articles on environmental factors in IBD, no consensus exists regarding which factor contributes most to trigger the onset of IBD. Identification and recognition of major environmental factors are prerequisite for effective disease treatment and prevention. Representative environmental factors such as smoking, breastfeeding, nonsteroidal anti-inflammatory drugs, antibiotic use in childhood, oral contraceptives, and appendectomy do not correlate with disease onset in most patients with IBD. In contrast, diet appears to be important in most cases of IBD. Diets rich in animal protein (risk factor) and deficient in dietary fiber (preventive factor) are characteristic of westernized diets in affluent societies. Recent research shows that westernized diets are associated with a reduced gut microbial diversity (dysbiosis), which may result in increased susceptibility to IBD and other common chronic diseases. Plant-based diets rich in dietary fiber are associated with increased microbial diversity. Recent reports on IBD therapy that replaced westernized diets with plant-based diets achieved far better outcomes than those previously reported in the literature. We believe that westernized diet-associated gut dysbiosis is the most ubiquitous environmental factor in IBD. Adoption of this concept may have the potential to provide a better quality of life for patients with IBD.

INTRODUCTION

The incidence of inflammatory bowel disease (IBD), a collective term for Crohn disease (CD) and ulcerative colitis (UC), has been increasing over time and expanding to different regions around the world, indicating that IBD is a global disease.1-6 Gut inflammation does not occur in the absence of gut microbiota.7 A dysregulated immune response to commensal bacteria may greatly contribute to IBD incidence and subsequent morbidity.

Like many other diseases, IBD is a multifactorial disease that occurs when genetic factors in a susceptible person are triggered by environmental factors. Recent genomewide association studies identified 200 susceptible loci involved in IBD.4 They are largely involved in 3 areas. The first area is related to innate immunity and autophagy (eg, NOD2, ATG16L1, IRGM, LRRK2). Namely, they recognize and clear microbial agents. The second is related to the adaptive immunity of interleukin-23 signaling and T-helper 17 cells (eg, IL23R, IL12B, STAT3, JAK2, TYK2) and interleukin-10 signaling (IL10). They regulate inflammatory response. The third is related to epithelial barrier function (eg, ECM1, CDH1, HNF4A, LAMB1, GNA12). They maintain the mucosal epithelial barrier against microbial invasion. The first appears to be implicated in CD only and the third in UC only. The second appears to be implicated in both CD and UC. These findings provide insight into the pathogenesis of IBD.8 It is obvious now that susceptible genes for IBD differ by ethnicity.9 In addition, it was recently demonstrated that host genetics influenced the composition of the gut microbiota. For example, healthy individuals with IBD-susceptible genes (NOD2, CARD9, ATG16L1, IRGM, and FUT2) exhibited a decreased abundance of Roseburia spp.9 Despite remarkable advances in genetics, the contribution of genetics to the onset of IBD is limited. Genetic–risk polymorphisms explain less than one-third of the heritability of the disease.4 Because the human genetic constitution has barely changed during its long history, the rapid increase in IBD incidence during the transition from a “developing” to “developed” nation can be explained not by genetic factors but by changes in environmental factors. It is recognized that a major driver of the growing incidence of IBD is westernization of lifestyle. However, the only lifestyle change recommended in current IBD guidelines is that patients with CD not smoke.3 Dysbiosis of the gut microbiota has been observed in IBD,1-3,4-6 and it is apparent now that gut microbiota is influenced by our diet. Thus, it seems critical to maintain gut symbiosis for the suppression of gut inflammation by consuming a suitable diet. With a suitable diet, substantial improvement in the prognosis can be anticipated. We believe that the lack of a suitable diet is the biggest issue faced in current IBD treatment. There are 2 steps to establishing a suitable diet for IBD. The first step is the recognition of the key factor (ie, westernized diet) among a variety of environmental factors in IBD, and the second step is investigation of a suitable diet for IBD. This commentary is not the first step to try to recognize westernized diet as the key environmental factor in IBD.

Several review articles on environmental factors in IBD have been published since 2016.1,4,6 Abegunde et al1 listed environmental factors under the headings lifestyle, pharmacologic agents, surgery, and so on. The European Crohn’s and Colitis Organisation Environmental Factors Working Group7 provided 22 evidence-based guidelines for current clinical practice. van der Sloot et al8 quantified environmental factors and listed them by exposures during life stages (childhood exposures, adolescence, young adulthood, and middle age).

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Keywords: Crohn disease, genetic factors triggered by environmental factors, inflammatory bowel disease, plant-based diets, polygenic disease, ulcerative colitis, western diet, westernized diet-associated gut dysbiosis
adulthood exposures, and lifelong exposures). Bernstein\(^4\) focused on factors relating to the gut microbiota. Kaplan and Ng\(^2\) proposed cutting the global incidence of IBD by 50% by 2032, which is exactly 1 century after the first description of CD in the literature in 1932. However, no statement was found in these reviews regarding the specific environmental factor or factors that may contribute the most to trigger IBD onset. This is most likely because of the current lack of firm evidence identifying the greatest environmental factors. Without recognition of key environmental factors, clinicians will continue conventional medical care which is inadequate and nonoptimal. Therefore, identification of the environmental factor most responsible for IBD is critical for treatment and prevention.

We previously reported in 2011 that diet-associated gut microbiota is the greatest environmental factor in IBD.\(^10\) We have been treating patients with IBD on the basis of this concept.\(^11\)\(^\text{-}\)\(^14\) The more we practice, the more we are convinced of the utility of diet-based therapy in IBD. In addition, there is growing evidence in the medical literature concerning the sequence of diet, gut microbiota, and health, which further supports our view.\(^15\) In this commentary, we describe why we think the greatest environmental risk factor in IBD is westernized diet-associated gut microbial dysbiosis.

### RECOGNITION OF INFLAMMATORY BOWEL DISEASE AS A LIFESTYLE DISEASE

The etiology of IBD has been described as unknown. The term idiopathic is often added: Idiopathic IBD. As already described here, we believe it is clear that westernized lifestyle is a major driver of the growing incidence of IBD. Other common chronic diseases are also lifestyle related (eg, obesity, diabetes, coronary artery disease, stroke), and IBD is probably no exception. If the cause of the disease is unknown, we cannot do anything more than conventional treatment. If the disease is related to lifestyle, lifestyle modification may prevent initiation of the disease process or possibly improve the disease course.

### CURRENT PROBLEMS IN INFLAMMATORY BOWEL DISEASE

No recommendation for lifestyle modification is stated in the guidelines except for nonsmoking for patients with CD.\(^3\) It is noteworthy that smoking is firmly appreciated as a risk and exacerbating factor in CD. Recent study in Eastern Asian countries, however, did not reproduce the results found in Western countries.\(^2\) The most common question asked by patients with IBD is what should I eat? Clinicians cannot adequately answer this question. The lack of identification of the key environmental factor is the biggest problem in current IBD practice. If it is identified, modification of the implicated lifestyle may improve disease outcomes.

### MOST UBQUITOUS ENVIRONMENTAL FACTOR IN INFLAMMATORY BOWEL DISEASE

Common environmental factors in IBD found across the recent reviews\(^1\)\(^\text{-}\)\(^6\) are listed in Table 1. Among the factors in Table 1, 4 criteria may be helpful in identifying the most important environmental factor. First, the factor should be a protective factor or a risk factor in both UC and CD. Second, the factor should be a protective factor or risk factor in all geographic areas. Third, most patients with IBD should be exposed to the factor. Finally, the factor should influence gut microbiota considering that gut microbial dysbiosis is consistently observed in IBD.\(^1\)\(^\text{-}\)\(^3\)\(^,\)\(^5\)\(^,\)\(^6\)

The epidemiology of IBD is similar in both CD and UC. This means that the role of the most ubiquitous environmental

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**Table 1. Environmental factors in inflammatory bowel disease (IBD)**

<table>
<thead>
<tr>
<th>Environmental factor</th>
<th>Role in IBD</th>
<th>Exposure to most patients with IBD</th>
<th>Relevance to gut microbiota</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UC</td>
<td>CD</td>
<td>Mode of role</td>
</tr>
<tr>
<td>Lifestyle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>P</td>
<td>R</td>
<td>Divergent in IBD</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal protein</td>
<td>R</td>
<td>R</td>
<td>Identical in IBD</td>
</tr>
<tr>
<td>Dietary fiber</td>
<td>N</td>
<td>P</td>
<td>Neither identical nor divergent</td>
</tr>
<tr>
<td>Tea or coffee</td>
<td>P</td>
<td>P</td>
<td>Identical in IBD</td>
</tr>
<tr>
<td>Low levels of vitamin D</td>
<td>R</td>
<td>R</td>
<td>Identical in IBD</td>
</tr>
<tr>
<td>Breastfeeding(^*)</td>
<td>P</td>
<td>P</td>
<td>Identical in IBD</td>
</tr>
<tr>
<td>Pharmacologic agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td>R</td>
<td>R</td>
<td>Identical in IBD</td>
</tr>
<tr>
<td>Antibiotics in childhood</td>
<td></td>
<td></td>
<td>Divergent among ethnic groups</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>R</td>
<td>R</td>
<td>Identical in IBD</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 inhibitors</td>
<td>R</td>
<td>N</td>
<td>No</td>
</tr>
<tr>
<td>Vaccination</td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Other factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendectomy</td>
<td>P</td>
<td>R</td>
<td>Divergent in IBD</td>
</tr>
<tr>
<td>Air pollution</td>
<td>R</td>
<td>R</td>
<td>Identical in IBD</td>
</tr>
</tbody>
</table>

CD = Crohn disease; N = neither protective nor risk factor; NSAID = nonsteroidal anti-inflammatory drug; P = protective factor; R = risk factor; UC = ulcerative colitis.

\(*\) Being breastfed as a baby is a protection against the development of IBD. Duration of breastfeeding is not specified.
factor in IBD should not be divergent between UC and CD but should be common to both UC and CD. Smoking and appendectomy have a divergent role in IBD; each is a protective factor for UC but a risk factor for CD (Table 1). Therefore, these are not the key factor. It is noteworthy that some environmental factors identified in Western countries are not the same in Asia. For example, antibiotic use in childhood is a risk factor for IBD in Western countries, but it is found to be a protective factor in recent Asian studies. Similar to the role of the environmental factors in UC and CD, the role of the key environmental factor is not divergent but must be identical across geographic areas. Therefore, antibiotic use in childhood is not the key factor.

According to the hygiene hypothesis, an improvement in sanitation with limited exposure to microbes results in impaired immune response, causing immune-mediated diseases including IBD. Hygiene factors studied include sanitary facilities (toilet, water supply), family size and birth order, pets, and farm animals. There is insufficient evidence to support or refute the hygiene hypothesis. A positive association between urban air pollution and IBD has been described. However, it is difficult to interpret whether IBD is a direct consequence of pollution. Although stress and anxiety are shown to be related to IBD relapse, they have not been proved to be risk factors for the development of IBD.

The most ubiquitous environmental factor for IBD should be present in most patients with IBD. Low levels of vitamin D, breastfeeding, nonsteroidal anti-inflammatory drugs, oral contraceptive use, dipeptidyl peptidase-4 inhibitors, air pollution, and Helicobacter pylori infection—all on the list (Table 1)—do not apply to the majority of patients with IBD. The remaining factor in the list in Table 1 is diet. All patients with IBD are exposed to food. Although dietary fiber is protective for CD, its protective effect is absent in UC. Animal protein is a risk factor for IBD. Diet influences gut microbiota. Namely, diet meets all 4 conditions for the key environmental factor. Increased consumption of animal protein and decreased consumption of dietary fiber are characteristic of dietary westernization.

Wealth inevitably induces dietary westernization, which explains the high incidence of IBD in wealthy nations. It can be concluded that a westernized diet is the critical environmental factor in IBD. 

**RATIONALE FOR HOW WESTERNIZED DIET CAUSES INFLAMMATORY BOWEL DISEASE**

Research on the gut microbiota has advanced our understanding about the key role of the gut microbiota in health and disease. The diseases extend beyond the confines of the gut (IBD) to various chronic diseases: Obesity, diabetes, coronary artery disease, stroke, rheumatoid arthritis, cancer, psychiatric diseases, and others. Gut microbiota is beginning to be recognized as an endocrine organ. The gut microbiota affects the immune system, host metabolism, cardiovascular system, enteric nervous system, brain and behavior, and stress/hypothalamic-pituitary-adrenal axis. Microbial diversity plays an important role in gut and systemic homeostasis. Reduced microbial diversity (dysbiosis) is commonly observed in a variety of chronic diseases, including IBD. In patients with IBD, bacterial levels are known to fluctuate up and down compared with healthy controls. Numbers of Fusobacterium, adherent-invasive Escherichia coli and Enterobacter organisms are increased, and Firmicutes and Bacteroidetes phyla, Faecalibacterium prausnitzii, Roseburia hominis, Bifidobacterium, and Prevotella are decreased. We tend to recognize things outside the body as environmental factors. However, the gut microbiota inside the body has been identified as an environmental factor for obesity. The presence of gut microbiota is a prerequisite for gut inflammation. Furthermore, it is also known that the gut microbiota is formed by our diet.

Recently, research is unraveling the relationship between diet and microbial diversity. We have coevolved with gut microbiota to exist in a symbiotic relationship. Westernized diets tend to cause gut dysbiosis (reduced microbial diversity), resulting in poor production of microbial metabolites such as short-chain fatty acids, which have diverse effects in maintaining homeostasis. In addition, these diets promote expansion and activity of colonic mucus-degrading bacteria, resulting in barrier dysfunction. In contrast, a plant-based diet rich in dietary fiber increases microbial diversity and produces beneficial microbial metabolites. These observations indicate that westernized...
diets increase susceptibility to not only IBD\textsuperscript{6}\textsuperscript{6} but also other chronic diseases. The precise mechanisms underlying how diet induces microbial dysbiosis and results in onset of individual chronic diseases are not yet fully understood.

There have been many schemas of the pathogenesis of IBD together with environmental factors. Most of them depict factors in parallel without indicating the degree of contribution to the pathogenesis. The schema for clinicians should be simple but provide clear information. Our schematic pathogenesis is presented in Figure 1. This schema is a modification of the original.\textsuperscript{10}

**CLINICAL OUTCOME OF MANIPULATING WESTERNIZED DIET**

Interventional studies to modify risk factors to reduce relapse or to improve patient outcomes are worthwhile. By replacing a westernized diet with a plant-based diet in treatment, we have achieved and published far better outcomes than those reported in both the active stage and remission stage in CD\textsuperscript{11,12} and in UC.\textsuperscript{13,14}

We now treat mild cases of UC with a plant-based diet first, not with medication.\textsuperscript{13,14}

It is clear that treatment based on the etiopathogenesis of the disease is optimal. Identification of the most ubiquitous environmental factor can lead to modification of the environmental factor. Our westernized diet is one of the major factors in current common chronic diseases. Plant-based diets are listed as variations of US Department of Agriculture healthy eating patterns and are recommended to the public to prevent common chronic diseases.\textsuperscript{20,21} The spread of a healthy diet may halt the further increase in IBD incidence or decrease the incidence. We know, however, that such spread is quite slow without a supportive public campaign such as the campaign against smoking.

We do not know how long it will take until the key environmental factor in IBD is firmly determined. Until then, we must analyze the available data for the second-best measure. As discussed earlier, the data point to westernized diet-associated gut microbial dysbiosis as the most ubiquitous environmental factor in IBD. Wide appreciation of this environmental factor by gastroenterologists will likely improve our therapeutic strategies and provide far better outcomes in IBD treatment.

**CONCLUSION**

We believe that westernized diet-associated gut microbial dysbiosis is the most ubiquitous environmental factor in IBD. Appreciation of this concept may help provide a better quality of life for patients with IBD.

**Disclosure Statement**

The author(s) have no conflicts of interest to disclose.

**Acknowledgment**

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**How to Cite this Article**


**References**


Family is not always about being comfortable. Case in point: “The Spinning Wheel of Doom.” That is not its real name, but that is the nom de guerre I give it. Also the “Wheel of Death” (after riding it the first dozen times).

You all know it: The small-time carnival comes to town with tinker-toy rides and easy-win (never-win) contests of skill. And there it is, lit up like a 1950s horror movie spaceship. The man (or woman) with the tattoos and gold tooth (or missing teeth) opens up the side door and you settle in to the 70s-era cushions. The walls spin faster and faster until you are pinned against the wall, and can even climb up it with aid of the G-force.

Now, once or perhaps twice is fine, but 20 times in a row, egged on by your 5- and 7-year-old children, stretches the parent-child bond. And when the operator of the ride nervously tells you, “You might consider taking a break,” you wonder if you are a good father or instead an enabler to your children’s self-destructive tendencies.

But at the end of the day, even after the vertigo has made you wish for stillness, the family bond is just that much stronger. And it could be worse: You could be that man or woman who runs the Wheel of Death 10 hours straight most days of the week, stationary in the center while the people at the inner walls of the ride circumnavigate you. Meanwhile, another world outside spins at one full turn of the planet each day.

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“Have you ever made a mistake?” I asked the Wise One, the one whom all the patients love. The Wise One is the “best doctor in town,” the experienced one, the one with gray hairs. The Wise One has monthly meetings with Rachel Naomi Remen, the guru of the art of healing.

“Yes,” said the Wise One. “I made a mistake once.” He bowed his head a little in—was it shame? “I remember it well,” he said. “It was years ago. A baby who was constipated. It took me 2 months to do the blood test—the baby had hypothyroidism. The parents blamed me for missing the diagnosis.”

Once? I thought. Though I was in the early years of my career, 2 or 3 years out of residency, I counted the mistakes I had made in the hundreds. Little ones, inconsequential. Near misses—whew, got lucky on that one. And then the big one. I was accused of having delayed the diagnosis of a serious illness in a child. I was devastated. The parents “fired” me. There was a threatened lawsuit, a meeting with “risk management,” a cordial and professional Q&A meeting.

It was deemed by the group (all pediatricians, much too nice) that there was no fault, it could have happened to anyone, but perhaps there was “some room for learning.” The family couldn’t find any expert witnesses and dropped the case. But I still didn’t have any way of knowing whether I had erred. It was too complex, hindsight a blinding light which had already rendered it impossible to look with objectivity on the way the case had played out.

And now, what to do with this?

“I made a mistake once,” the Wise One said.

If I’m the only one who makes so many mistakes, should I really be here?

But yet here I am, clocking in and clocking out every day. Nobody knows (do they?) that I might not be worthy of the power that I have been given through my medical degree.

Am I the only one who feels this way? 

How to Cite this Article

Accompanying artwork:
The Imposter by Caroline Shooner
A Ukulele Appears From Somewhere

Parwathi V Paniker, MD

E-pub: 01/24/2019
https://doi.org/10.7812/TPP/15-246

I've been busy in Hawaii for 6 months. I'm exhausted. Every Thursday I wake up at 3:45 am, ensure my travel bag is stocked, and head to the airport.

Flying to Oahu, renting a car, and staying in a hotel outside Waikiki has already lost its charm. I actually go directly from the airport to Mapunapuna Clinic to do surgery. I check into my hotel at 7:30 in the evening, gulp down some dinner, and fall asleep in front of my Kaiser laptop. Friday brings another day of surgery and—joy!—my trip home.

A particularly long and busy Friday finds me frantically negotiating the Nimitz freeway aiming for the Avis rental car return office.

The waiting area is packed. A local family with a young man, several aunts, and perhaps a grandfather stands smiling and chatting in the sun. Two very tan tourist ladies and their young female charges sit and squint in the direction of the shuttle bus. They wear gold and carry floral luggage. The 2 young women are 2-thumbing their iPhones. I admit I am judging them and scowling.

The patriarch of the local family tells the young man to help the tourist ladies with their luggage. He is one of those big, thick, handsome Polynesian boys. He hops to attention, and soon we are all on board.

The young man asks the tourists where they are from, but I don’t listen because I don’t care. He then asks the shuttle bus driver to turn off the radio because he will entertain our guests.

A ukulele appears from somewhere in the local family’s bundles. The young man begins to sing in a loud, sweet voice. It is a sappy Jack Johnson song or some such ballad. The tourists have put away their phones. They are no longer as irritating to me as they had been.

The local aunties start asking me where I live. They recommend that the tourist ladies visit Maui next time. The local family had just come over for a funeral. I resolve to smile at tourists more often.

How to Cite this Article

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Artist Information
Phil LaBorie is an artist living in Murrels Inlet, SC.
HOSPITAL CHAPLAIN

Chaplain, as I rush from patient room to patient room, sprinkle me with the dust that allows one to sit for long moments, silently, with another. I am exhausted attempting to outrun the predators Emotion and Guilt. I need to be present.

Chaplain, how do we treat you? Do you feel respected, or simply overlooked like so many on the “team”? Called off the bench when we starters have once again failed against a mightier opponent … “Here, your turn, you finish … .”

Chaplain, do you ever dream of trading your white collar for my white coat? Longing not for other abilities, but for lesser burdens?

HOUSEKEEPING

You hear the sobbing before the clinical staff are remotely aware. Patients held captive by fear and loneliness; you acknowledge their presence without power differentials—person to person. You remind me of our hospital unit’s MVP when I was an intern: “Clara the Cleaning Lady,” the wisest, most gentle member of our team.

Memories of her goodness continue to inspire me.
The monarch butterflies so abundant around the small pond are slowly disappearing. Tomatoes from the vine that curled its way up the drainage spout are now lined up on the kitchen windowsill to capture the sun's rays. Summer draws to an end as my father's life also draws to a close.

As part of my narrative, I have included, in italics, entries from my journal from this time.

MARCH 17, 7:55 PM
I am sitting next to Dad on a wooden chair as he lies sleeping in the hospice bed in the local private hospital. His wasted body is barely visible under the sheets. His arms rest on his chest as he lies on his back in exactly the same position I lie in each night. It’s somehow familiar and comforting. Every so often his breathing becomes erratic, and he pants with the exertion of keeping his body in this world. And then he is silent. I hold my own breath, waiting for the familiar sound of his breathing, alternating between wanting that breath to be his last and fearing it may be. I am anxious that my father not die alone in this small room and anxious he will die with just me here.

During the past few years, we have watched Dad slowly disintegrate. The losses were gradual but steady and devastating in their completeness. Major heart surgery offered him the possibility of a better quality of life, yet it never came to pass. The lethargy that had plagued him before the surgery remained. He became increasingly dependent on Mum for everything as he lost the ability to make a decision, give an opinion, help himself lying in bed. He never spoke about dying or what he wanted. I cannot comfort myself that we had a conversation that spoke deeply of a wife’s devotion, respect, dignity, and love.

It seems now that death is waiting close by in the wings.

MARCH 18, 8:12 PM
Tonight I sit in the dim glow of the night light and reflect on this man; my father for 51 years. His contribution to my life has been immense. When I took classes at the university in my late teens we had many heated discussions. Years later I realized he was encouraging me to think critically and defend my views on contentious issues. During the past decade the discussions we had concerned my research focus on the enormity of what we are asking: No fluids for more than a couple of days in his condition, in this heat, will almost certainly mean he will die by dehydration. If he dies within a few hours of stopping all fluids—unless he asks for them—will mean. I know I hold my dad’s hand, so parched and thin that deep hollows carve into the skin between his thumb and fingers. These hands that held my mother in loving embrace, and wrapped around his children in welcome and farewell, now grasp repeatedly and unconsciously at the sheets.

Vulnerability speaks clearly of confusion, frailty, wearing incontinence pads, having whatever meal is served up during the day no matter how carefully prepared, and being wheeled out to bed when routine dictates. It also speaks deeply of the kindness and gentleness of compassionate nursing care, a glass of cold lemonade or a bowl of vanilla ice cream, a joke to lighten the load, and being wheeled outside to enjoy the warming sun of a dying summer.

MARCH 20, 4:45 PM
My father’s blue eyes are milky and sticky, unable to focus, and now devoid of recognition. I comfort myself that my voice, reminiscing on the past, may ease any distress when he can no longer recognize who I am, but I know he is almost gone to this world. Perhaps he bears nothing.

Dad’s good clothes hang in the bedroom at home, his trousers dry-cleaned, shirt ironed, and shoes polished. Final loving acts that speak deeply of a wife’s devotion, respect, dignity, and love.

Dad has stopped being able to suck on a straw.

His funeral is prepared, the death notices written, groceries brought to make food for the morning and afternoon tea to be served during the open home when Dad comes home for the final time. My brother and sister arrive, and we spend Sunday morning out walking along the riverbank. Dad’s inability to suck seems another final step on this journey we are all on. We wonder aloud at what Dad might think of the situation if he were to witness himself lying in bed. He never spoke about dying or what he wanted. I cannot comfort myself that we had a conversation that clarified what was important to him at the end of life so that we would know what to do, so that we wouldn’t question every decision that needed to be made. Dad never discussed his health even when it became clear that he was not improving. Always a very private and proud man, Dad walked the final journey on his own.

We talk with Mum and call the hospice nurse to arrange a meeting. In a small room off the corridor we sit and discuss what stopping all fluids—unless he asks for them—will mean. I know the enormity of what we are asking: No fluids for more than a couple of days in his condition, in this heat, will almost certainly mean he will die by dehydration. If he dies within a few hours.
or a day, death will be the end result of his condition. I know that as Dad moves closer toward death, giving him fluids orally can be problematic if they pool in his throat, causing choking and possibly setting up an infection site, aspiration, and possible pneumonia. Intravenous fluids are futile given that he is dying. The clinical reason for acting to withhold fluids and the family’s decision are similar—to not prolong his dying, to act beneficently and humanely, and to allow Dad to die with some measure of dignity. Yet I grapple with the implications of withholding fluids and cannot escape the thought that in making this decision we are complicit in hastening his death.

MARCH 22, 8:30 PM

Around 4 pm Dad’s breathing became much more labored. He is now deeply unconscious. His chest heaves with the exertion of breathing. When I swab his mouth to keep it clean and moist, there is no sucking response at all.

I sit and hold his hand, talking to him quietly of memories we shared: Heading to the beach for a BBQ after work, camping holidays at the lake, taking the dog for a walk along the beach in winter, cooking sausages on a fire, car trips into the city each weekday morning; good memories of a happy, loving childhood.

I have a vision of my Nana and Pop preparing to welcome Dad home. While we are saying farewell, they are rejoicing that they will see their son again. “You can go, Dad,” I tell him. “Don’t worry about Mum, we’ll look after her.”

Dad died at 12:15 am on Tuesday, March 23. My fear that he would die alone did not happen. My fear that he would die when I was with him seemed to dissipate as I sat with him and his breathing slowly quietened and then stopped. It was quiet and peaceful and final. I was able to say goodbye and it felt right.

Since my father died, the questions I asked myself remain unanswered: By deciding to withhold fluids, were we complicit in hastening his death? Did we make the right decision? The answers are impossible to know beyond a shadow of a doubt. It is probable, given his physical deterioration during the preceding days, that he died of the underlying condition. But perhaps those 24 hours without fluids contributed to him dying sooner rather than later. I have come to realize that whether or not we hastened his death is irrelevant because the reason we chose to withhold fluids was acknowledgment that he was actively dying and it was time to let him go. Continuing to hydrate him may have prolonged the dying process and seemed an indignity to the way my father had lived his life.

EPILOGUE

Two years after my father’s death, I look back on the weeks we had together before he died with a deep sense of comfort and stillness. My father died in the way he wanted—privately, quietly, dignified, and on his terms. Although he never made his wishes clear about his medical preference regarding treatment, I believe that the values he held, combined with the way he led his life, were consistent with him agreeing with the family’s decision to withhold fluids. He would have wanted to spare my mother having to endure a slow dying process. He was also a very private man who had no choice but to accept the care of others. Although he was gracious in this, he was not comfortable with it.

But if he were alive today, perhaps he would be troubled by the recent events that have set in place a governmental process to discuss the legalization of assisted dying in New Zealand.1 Perhaps we would sit down together over a glass of wine, and he would question my support of the bill. We’d banter back and forth. I’d tell him that if he were dying, I’d respect his wishes about what he wanted. I’d hope he’d respect mine.

Disclosure Statement

Dr Malpas is a member of the End-of-Life Choice, Society of New Zealand, Inc (Waikanae, New Zealand). The author(s) have no other conflicts of interest to disclose.

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Reference


Survivors’ Affair

A man’s dying is more the survivors’ affair than his own.

— Thomas Mann, 1875-1955, German author, social critic, essayist and the 1929 Nobel Prize in Literature laureate
This comic is my response to a near-death experience that changed my life in big and small ways. It touches many topics in addition to medicine, and suggests how my view of life matured following it.

— Stephen Bachhuber, MD
The Great Wall

GET OUT OF BED! WE FLY TO TIBET TODAY.

IM NOT OK... NOT DIZZY, ON BEKRYN.

WE ARE AT 17,000 FEET!

GOT TO...
The Great Wall

Why am I back here? I was home!

Girl says you have an infection and a fever of 102. You are also dehydrated and agitated. Sick!

Otherwise in fine shape!

How much more do I need to drink today?

Keep going... you haven't fe'd in hours!

Fever's down. I feel much stronger.

I can't stay in this hotel room one more day!

We're both ready to go out.

Is spinning a prayer wheel really praying?

Now I think it is.

... I felt loved and comforted in God's arms. I didn't want to come back!

I'm just glad you're here!

Was it an iron lung dream, or another reality?

I don't know, but God the mother seems very real to me!

Answer: 4 liters
Section A.

**Article 1. (page 16) Patient Education and Pharmacist Consultation Influence on Nonbenzodiazepine Sedative Medication Deprescribing Success for Older Adults**

Which of the following statements about nonbenzodiazepine (Z-drug) use is false?

- a. Long-term Z-drug use among older adults is associated with falls, daytime sedation, and cognitive impairment
- b. Long-term use of Z-drugs may develop a dependence on these medications
- c. All patients, regardless of age, are at similar risk for adverse events following the use of sedative medications, like Z-drugs
- d. Z-drug use has not been shown to improve sleep over the long term

In this study, patients who received educational materials and a pharmacist consultation were:

- a. Significantly less likely to discontinue Z-drug use than patients who did not receive an intervention
- b. Just as likely to discontinue Z-drug use as patients who did not receive an intervention
- c. Significantly more likely to discontinue Z-drug use than patients who did not receive an intervention

**Article 2. (page 39) Feasibility of a Preoperative Anemia Protocol in a Large Integrated Health Care System**

Which is the best recommended management to treat iron deficiency anemia preoperatively?

- a. Oral iron supplements twice a day
- b. Intravenous iron infusion
- c. Oral iron supplement once a day to be taken with vitamin C
- d. Delay surgery until hemoglobin level is normalized

Which of the following is an incorrect statement regarding preoperative anemia?

- a. Optimizing preoperative anemia is a required component of the Joint Commission’s Certification in Patient Blood Management
- b. Existing preoperative anemia programs include all types of operations
- c. Preoperative anemia is a key component of Enhanced Recovery After Surgery
- d. Preoperative anemia protocols enhance the early recognition and timely treatment of anemia
- e. Mild levels of preoperative anemia are associated with increased perioperative morbidity and mortality

**Article 3. (page 70) Osteonecrosis of the Hip: A Primer**

Which of the following statements is true?

- a. Current evidence recommends that adolescent patients sit upright or stand against the examination table during vaccination
- b. ON is a condition characterized by a tendency to affect the hip and knee joints
- c. Breathing exercises
- d. In Ficat Stage I, in radiographs that reveal no evidence of ON, an MRI is needed to confirm the diagnosis
- e. The main associated risk factor for atraumatic ON is overexercising
- f. Caffeine consumption
- g. Managing patients with ON of the hip with nonsurgical modalities for as long as possible is generally the best standard of care
- h. Intravenous iron infusion
- i. Verbal education
- j. Social support or distraction

**Article 4 (online) Development of an Intervention to Reduce Pain and Prevent Syncope Related to Adolescent Vaccination**

Which of the following was NOT cited by practitioner, adolescents, or parents as a desirable intervention to reduce pain or syncope following vaccination among adolescents?

- a. Verbal education
- b. Social support or distraction
- c. Caffeine consumption
- d. Breathing exercises
- e. Intravenous iron infusion
- f. Intravenous iron infusion
- g. Intravenous iron infusion
- h. Intravenous iron infusion
- i. Intravenous iron infusion
- j. Intravenous iron infusion

Which of the following statements is true?

- a. Current evidence recommends that adolescent patients sit upright or stand against the examination table during vaccination
- b. Reactions to vaccines—such as acute injection site pain, dizziness, and fainting—are barriers to the initiation and completion of recommended vaccination schedules among adolescents
- c. When 2 vaccines are being given at the same time, practitioners should administer the least painful vaccine first
- d. As a recent clinical trial found that water consumption does not affect the occurrence of fainting after vaccination
- e. Current evidence recommends that adolescent patients sit upright or stand against the examination table during vaccination
- f. Reactions to vaccines—such as acute injection site pain, dizziness, and fainting—are barriers to the initiation and completion of recommended vaccination schedules among adolescents
- g. When 2 vaccines are being given at the same time, practitioners should administer the least painful vaccine first
- h. As a recent clinical trial found that water consumption does not affect the occurrence of fainting after vaccination
- i. Current evidence recommends that adolescent patients sit upright or stand against the examination table during vaccination
- j. Reactions to vaccines—such as acute injection site pain, dizziness, and fainting—are barriers to the initiation and completion of recommended vaccination schedules among adolescents
- k. When 2 vaccines are being given at the same time, practitioners should administer the least painful vaccine first
- l. As a recent clinical trial found that water consumption does not affect the occurrence of fainting after vaccination
- m. Current evidence recommends that adolescent patients sit upright or stand against the examination table during vaccination
- n. Reactions to vaccines—such as acute injection site pain, dizziness, and fainting—are barriers to the initiation and completion of recommended vaccination schedules among adolescents
- o. When 2 vaccines are being given at the same time, practitioners should administer the least painful vaccine first
- p. As a recent clinical trial found that water consumption does not affect the occurrence of fainting after vaccination

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Section B.

**Objective 1**
Integrate learned knowledge and increase confidence/confidence to support improvement and change in specific practices, behaviors, and performance.

<table>
<thead>
<tr>
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**Objective 2**
Lead in further developing “Patient-Centered Care” activities by acquiring new skills and methods to overcome barriers, improve physician/patient relationships, better identify diagnosis and treatment of clinical conditions, as well as, efficiently stratify health needs of varying patient populations.

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**Objective 3**
Implement changes and apply updates in services and practice/policy guidelines, incorporate systems and quality improvements, and effectively utilize evidence-based medicine to produce better patient outcomes.

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Section C.

What other changes, if any, do you plan to make in your practice as a result of reading these articles?

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Section D. (Please print)

Name ____________________________
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The Permanente Journal • Winter 2019

ORIGINAl RESEARCH & CONTRIBUTIONS
4 Challenges and Successes with Food Resource Referrals for Income-Fourteen Patients with Diabetes. Serajna Marpajda, MSC, Alicia Fernandez, MD, Jaelle Lupo, Audrey Tang, NP, Hillary Seligman, MD, BSc, Elizabeth J Murphy, MD, DPH
In semistructured phone interviews with twelve income poor patients in a diabetes clinic affiliated with a safety net hospital, the prevalence of food insecurity was high (68%). Provision of written and verbal information alone about community food resources resulted in few linkage rates (2-6%), even with individually tailored referrals. Misperceptions about eligibility, fear around government program regulation, inaccessibility, lack of information retention, competing priorities, an inability to cook, stigma, and a perceived sense of shame were major barriers to use. Personal-guided, clinic-referred entitlement to a food resource facilitated a higher connection rate (31%).
32 Liansong Chen, MD
To remember the worst wildfire in California history, the artist took thousands of photos in the community, around the Santa Rosa Medical Center. From the artist: “Time flies, the disaster occurs here and there year after year. I wish for rebuild starts. The disaster occurs here and there, year after year. I wish for rebuilding starts.”
Dr Chen is Medical Director and a Pathologist at the Santa Rosa Medical Center in CA. More of Dr Chen’s photographs can be seen in this issue of The Permanente Journal.

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The Heroin Diaries: A Book of Poems – Little Stories to Understand Why
Mary Smed, MD
ISBN 978-0-9770463-7-9
Portland, OR; Oakland, CA: The Permanente Press; 2017 Paperback: 75 pages $19.95

26 Gabapentin and Cancer Risk: Updated Findings from Kaiser Permanente Northern California. Gary D Friedman, MD, PhD, Niran Asharchoos, MD, Lauren A Habib, PhD
Updated analyses with 7.5 years of follow-up show little if any evidence for carcinogenic effects of gabapentin. All odds ratios for 3 or more and 8 or more prescriptions were moderately reduced by control for smoking and alcohol. Sensitivity analyses did reveal a markedly increased risk of vaginal cancer in gabapentin users with epilepsy compared with users without epilepsy.

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