

Research News Quarterly

DECEMBER 2019

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EDITOR

VEENA ANTONY, MD

Chair, Research Advocacy Committee

ADVISORY BOARD MEMBERS:

AMALI SAMARASINGHE, Ph.D.

Member, ATS Research Advocacy Committee

NUALA S. MOORE

Director of Government Relations

Letter from the Editor

Our feature article this month is a commentary by Drs. Laszlo T. Vaszar, M.D. and Karen L. Swanson, D.O. of the Mayo Clinic on the current state of knowledge on lung injury associated with the use of e-cigarettes. In the article, Drs. Vaszar and Swanson discuss the potential causes of these illnesses and injuries and the current state of research in the area. Continuing on the subject of vaping-associated illnesses, next we have a report on new research funding opportunities available through a Notice of Special Interest (NOSI) from several NIH institutes including NHLBI, NIEHS, NIDA, NIAID and NCI. The article details some of the applicable research questions that can be addressed through the NOSI. **The application deadline for these opportunities is February 27, 2020.**

Research Advocacy Committee member Nizar Jarjour, M.D., provides an introduction to NHLBI’s PrecISE Network, which aims to initiate a new era of personalized precision medicine for individuals with severe asthma, followed by a brief update on NHLBI’s efforts to update the National Asthma Education and Prevention Guidelines.

Next, we move to PCORI, where we report on a new PCORI-funded study, led by former ATS President J. Randall Curtis, M.D., MPH, showing improved patient satisfaction with end-of-life care goals through use of a survey tool, followed by efforts to legislatively renew PCORI, including its funding.

Moving to news from Washington, DC, we report on events coordinated by ATS and partners for former NIEHS Director Linda Birnbaum, Ph.D., who retired in early October 2019. We round out the Quarterly with the latest report from our Washington Office on 2020 federal health research funding.

Sincerely,

Veena Antony, MD

Editor

Chair, Research Advocacy Committee



QUARTERLY FEATURE: VAPING-RELATED INJURY

E-Cigarettes: A Rapidly Evolving Challenge

By **Laszlo T. Vaszar, M.D.** and **Karen L. Swanson, D.O.**

Mayo Clinic

Division of Pulmonary Medicine, Phoenix, Arizona

We have witnessed an explosion of media interest since the publication in August 2019 of a cohort of 53 e-cigarette users from Wisconsin and Illinois who presented with respiratory, gastrointestinal, and constitutional symptoms, and bilateral infiltrates on chest imaging.ⁱ One patient died while 94% of the cohort were hospitalized, and 32% required intubation and mechanical ventilation. Although a wide variety of vaping products and devices were used by this group, 84% vaped tetra-hydrocannabinol (THC), the active ingredient of marijuana.

As of November 20, 2019, the CDC has received reports of 2,290 cases of, and 47 confirmed deaths from electronic cigarette or vaping product use-associated lung injury (EVALI), a newly described illness with poorly understood pathophysiology.ⁱⁱ Responding to the rising number of reported cases, the CDC published interim guidance to diagnose severe pulmonary disease associated with e-cigarettes.ⁱⁱⁱ A “confirmed” case of EVALI requires: 1) use of an e-cigarette or vaping device within 90 days of symptom onset; 2) presence of pulmonary infiltrates; 3) absence of clinical and laboratory evidence of infection; and 4) absence of evidence for alternative diagnoses (e.g. cardiac, rheumatologic, or neoplastic processes). Criteria for a “probable” case of EVALI are identical with the exception of the third criterion. A coexistent infection does not rule out probable EVALI if the clinician does not believe infection is the sole cause of respiratory illness or minimum criteria for ruling out infection have not been met.

The common occurrence of marijuana products in the reported use history of EVALI patients has raised concerns that lipid solvents or additives, such as vitamin E oils, are causally implicated in EVALI. Supporting this hypothesis is the finding of vitamin E acetate in all 29 patients with EVALI whose BAL samples were analyzed by the CDC.^{iv}

The lipid pneumonia hypothesis was challenged however, by a review of 17 lung biopsies from patients with EVALI published by our group at Mayo Clinic.^v None of these cases showed histologic evidence of exogenous lipid

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Quarterly Feature: Vaping-Related Injury *(Continued from page 2)*

pneumonia. Instead, the pathology pattern was that of an airway-centered chemical pneumonitis from one or more inhaled toxic substances.

While it is likely that no single cause will emerge as the exclusive etiology of EVALI, the list of plausible toxin candidates currently includes, in addition to vitamin E acetate:

- Myclobutanil, a fungicide used in marijuana farming and present in recreational marijuana that turns into hydrogen cyanide when burned;
- Pulegone, a carcinogenic oil that occurs naturally in plants including peppermint and pennyroyal and was used in a synthetic form as a minty flavor until it was banned as a food additive by the FDA in 2018;^{vi}
- Diacetyl, a flavoring in popcorn that is associated with bronchiolitis obliterans. A 2016 article reported the finding of diacetyl in levels exceeding the laboratory limit of detection in 39 of the 51 e-cigarette flavors tested.^{vii}

E-cigarettes have been widely available in the US for only about a decade but have already emerged as the most commonly used tobacco products among teenagers, with a rising prevalence (21% of high schoolers, but only 3% of adults reported current use of e-cig in 2018). Most reports have identified acute, rapidly progressive, severe or life-threatening pulmonary consequences of short-term use of vaping products. Insufficient time has passed to assess the long-term consequences of e-cigarette use. The vast heterogeneity of inhaled mixtures, some of uncertain origin, with unknown and difficult to trace contents, increase the challenge to investigators as well as those at the front-line healthcare delivery, public health, and regulatory levels.

Approaching vaping with an analytical frame similar to that used in conventional cigarette use is probably misguided because vaping is associated with toxicity following short

term use, binge behaviors, and heterogeneity of mixtures with unknown ingredients. The e-cigarette-using community also likely consists of multiple subcultures that will require different approaches from healthcare providers and public health officials. A recent Norwegian study identified a subculture of pragmatic users (whom the authors labelled “substitutes”) who rely on e-cigarettes to

quit smoking, and another of “cloud chasers” who derive a sense of belonging from the vaping community, identify with its symbols and lifestyle, and are politically mobilized to influence vaping regulation.^{viii}

The growth of e-cigarette use has created a rapidly evolving arena in which mechanistic pathways, optimal clinical management, assessment of long-term natural history, public health implications, and regulatory responses remain to be fully defined. ■

NEW FUNDING OPPORTUNITIES!

NIH Releases Funding Opportunities on Vaping-Associated Lung Injury

The crisis in vaping-associated deaths and injuries around the country points to the urgent need for expanded research on the causes, development and treatment of both these illnesses and all of the health effects of e-cigarettes, as well as prevention. On November 6, 2019, NIH released a [Notice of Special Interest \(NOSI\)](#) that invites research on the causes, mechanisms, and long-term prognosis of individuals with e-cigarette or vaping associated lung injuries. The NOSI, issued by 6 NIH institutes including the NHLBI, NIEHS, NIDA and NCI, announces the availability of funding opportunities for administrative supplements and competitive revisions to active funded grants to study research questions related to vaping associated lung injury (EVALI) and related health effects of vaping.

NIH notes special interest in studies that utilize human research or unique model systems investigating the consequences of vaping. The grant opportunities may be used for collection of lung samples from human cohorts of individuals who vape and/or development of novel model systems to expose animals and cells to e-cigarette aerosols and aerosol constituents. Proposed studies should have substantial public

health impact and contribute to exploration of this vaping-related illness, including diagnosis, treatment and prevention.

The application deadline for these opportunities is February 27, 2020 at 5pm local time of the applying organization. Researchers intending to submit an application are strongly encouraged to discuss their proposed research/goals with a Program Officer from an appropriate Institute or Center listed in the NOSI in advance of the application deadline in order to determine suitability and relevance of individual institutes or Centers.

The NOSI outlines over a dozen different research questions that could be investigated under these grant opportunities, including:

- Are there population-specific contributions for susceptibility to health effects of vaping such as EVALI; e.g. based on age, gender, pregnancy status, or comorbid psychiatric or other health conditions? Based on current case reports, applications exploring health effects in younger populations are strongly encouraged.
- Are there individual susceptibility factors that influence risk for developing disease after potentially causative e-cigarette exposures?
- Are there any health effects associated with secondary or environmental exposures to e-cigarette aerosols?
- What can we learn about mechanisms involved in the development of health outcomes of vaping, including EVALI? How do the agents in e-liquids, including thermal degradation products, affect the inflammatory state of pulmonary epithelia, endothelia, or immune cells?
- How can vaping-related health outcomes, such as EVALI, be treated? ■

ASTHMA

NHLBI's PrecISE Network Aims to Help Launch Era of Personalized Precision Medicine for Patients with Severe Asthma

By **Nizar N. Jarjour, M.D.**, member,
ATS Research Advocacy Committee

Despite treatment with high dose inhaled corticosteroids and a second controller therapy, many patients with asthma continue to have poor symptom control, low lung function, and/or recurrent asthma exacerbations. These patients have severe asthma. Severe asthma affects 5 - 10% of all patients with asthma (2-3 million Americans) and is associated with a disproportionate share of asthma-related morbidity, mortality, and healthcare utilization. Although patients with severe asthma may present with similar clinical symptoms, there is significant heterogeneity in disease etiology, pathobiology, and manifestations.

The PrecISE (Precision Interventions for Severe and/or Exacerbation-Prone) Asthma Network was established by the National Heart, Lung, and Blood Institute in 2018 to test novel interventions in biomarker-defined subgroups of patients with severe asthma. The PrecISE Network will use an adaptive platform trial design conducted under a single master protocol to identify new therapies that are effective in biomarker-defined subgroups of severe asthma. Up to six novel therapies will initially be included, with new therapies added as they become available. The adaptive platform trial design will enable assessments of multiple interventions as well as the utility of biomarkers in predicting treatment response. Interventions may be discontinued and new interventions added over time, as data accrue on the safety and efficacy of the various interventions. Additionally, the biomarker-based definitions of target subgroups for each intervention may be adapted during the study.

Following the screening period, participants will be randomly assigned to interventions based on their biomarker profile and enter a series of 16-week double-blind crossover treatment periods separated by 8 to 16-week washout periods. Participants will be randomly assigned to placebo interventions to help maintain masking of treatment assignments. There are 3 primary efficacy endpoints to assess treatment response: 1) Forced expiratory volume in the first second (FEV1) percent predicted; 2) Asthma symptom control based on Asthma Control Questionnaire-6, and 3) CompEx events, a composite end point of clinically relevant deteriorations and severe exacerbations.

Enrollment in the PrecISE study is expected to start in late 2019, and the study will continue for 42 months. The PrecISE Network will help to launch a new era of personalized, precision medicine in severe asthma. Approximately 35 U.S. and two international sites will enroll 800 adult and adolescent (12-17 years of age) participants with severe asthma and who are currently uncontrolled or continue to have exacerbations. Participants must be on a stable regimen of asthma medications, and they need to meet a number of inclusion/exclusion criteria.

For more about the PrecISE study, go to the website at www.preciseasthma.org or follow PrecISE on Twitter: @preciseasthma.

NHLBI Working on Updating Asthma Guidelines

The NHLBI is moving forward on updating the 2007 National Asthma Education and Prevention Program (NAEPP) guidelines. [An Expert Panel report on the guidelines](#) is now out for public review with a comment deadline of January 17, 2020.. Following the closing of the public comment period, the institute will review the public comments and make any determined revisions and will then present the revised draft guidelines at the American Academy of Allergy, Asthma and Immunology (AAAAI) Annual Meeting in Philadelphia, PA March 13 – 16. After additional review and update, the institute expects to publicly release the final NAEPP guidelines in the Fall of 2020. The ATS will comment on the NAEPP Expert Panel report and throughout the process for updating the guidelines. ■

NEWS FROM PCORI

New PCORI-Funded Study on End-of-Life Care Communication Shows Improved Patient Satisfaction with Use of Survey Tool

The Patient-Centered Outcomes Research Institute (PCORI) recently featured a new study funded by the institute that shows improved patient satisfaction through use of a survey tool to facilitate discussions among patients and clinicians about end-of-life care goals. [The study](#), led by former ATS President J. Randall Curtis, MD, MPH, at the University of Washington, was highlighted in a November PCORI update as part of the institute's aims to provide patient-friendly postings on of its funded studies, including study results summaries, final research reports and journal articles.

In the study, 537 patients with serious illnesses including cancer, lung disease or other serious health problems completed a form about their care goals and their preferences for discussion of these goals. The study included 132 primary care doctors, specialists, and nurse practitioners from clinics in Washington State. The research team compared communication and care for two groups. In one group, patients, doctors, and families saw information from the form before a visit. The other group didn't see the results. Patients in both groups filled out follow-up surveys two weeks, three months, and six months after their initial office appointment.

Study Results

Compared with the group that didn't see the results of the form, the patients in the group that did see the form:

- Were more likely to talk with their doctors about goals for care
- Reported better communication with their doctors

- Were more likely to report receiving care in line with their goals, as long as those goals didn't change later in the study

ATS Joins Effort Supporting PCORI Renewal

The ATS joined a recent [Friends of PCORI letter to Congress](#) urging renewal and funding for the research agency. PCORI which supports patient-centered comparative effectiveness research, is in need of legislative renewal — called, “reauthorization” — following expiration of its original authority this year. The letter, signed by over 200 patients, providers, and academic organizations, urges Congress to enact first a temporary spending measure to continue PCORI's funding through the end of the year, as well as a full five-year renewal of the institute, including needed funding over this period. The Friends of PCORI letter notes that in its first decade of existence, the institute has supported over 700 research studies, totaling approximately \$2.4 billion across 44 states, on the best treatment approaches and effective interventions to make our health system more efficient and fully engage patients through the research process. ■

NEWS FROM NIEHS

ATS Convenes Capitol Hill Events for Retiring NIEHS Director Linda Birnbaum

On September 24, 2019, the ATS and partners in the Friends of NIEHS, including the Endocrine Society and the American Lung Association, held events on Capitol Hill to honor retiring NIEHS Director Linda Birnbaum, Ph.D. The Friends of NIEHS held a lunchtime education briefing for congressional staff in the U.S. Senate entitled, A Healthy Start for Every Child: How the Environment Influences Health and Development. The briefing featured speakers Linda Birnbaum, ATS member Nadia Hansel, M.D., Associate Dean for Research and Director of the Division of Pulmonary and Critical Care at Johns Hopkins Medicine in Baltimore and Joseph Braun, RN, Ph.D., Associate Professor of Epidemiology at Brown University.

Dr. Birnbaum gave an overview of NIEHS's expansive research portfolio in child health and development while Dr. Brown presented on the impacts of per and polyfluoroalkyl (PFAS) exposures through drinking water to child health and development. Dr. Hansel discussed her research findings on the respiratory health effects of indoor and outdoor pollution to children, including asthma exacerbations, and additionally the linkages to adult respiratory diseases such as COPD. Drs. Braun and Hansel called on Congress to support increased funding for NIH to expand this critical science.

In the evening, the Friends of NIEHS held a Congressional Reception in the U.S. House of Representatives, hosted by Congressman David Price (D-NC), to celebrate Dr. Birnbaum's decade of leadership at the NIEHS. Melissa Perry, ScD., MHS, Chair of George Washington University's Dept. of Environmental and Occupational Health, served as master of ceremonies. Congressman Price, who represents North Carolina's 4th congressional district which includes the NIEHS campus, presented Dr. Birnbaum with Congressional Record remarks he

made on the floor of the U.S. House in her honor. Fogarty International Center Director Roger Glass, M.D., also spoke, commending Birnbaum for her many accomplishments, including her leadership of the NIH research responses to the Gulf oil spill and natural disasters such as Hurricane Harvey her expansion of community-based participatory research and establishment of the NIEHS Clinical Research Unit.

Rick Woychik, Ph.D, the former NIEHS Deputy Director, will serve as Acting NIEHS Director until a permanent director of the institute is selected. ■



From left to right Former NIEHS Director Linda Birnbaum, Ph.D., Joseph Braun, Ph.D., Nadia Hansel, M.D., Nuala Moore, ATS Staff and Co-chair, Friends of NIEHS.

RESEARCH FUNDING

Congress Passes Short-Term 2020 Spending Measure, Averting Government Shutdown

In late November, Congress avoided a federal government shutdown and passed a short-term spending measure funding government programs until December 20, 2019 which the President signed into law. Congress and the Administration now have until December 20 to either finalize FY2020 spending or pass another short-term measure extending government spending into 2020. The measure also provides funding extensions through December 20 for community health centers, the National Health Service Corps., the Patient-Centered Outcomes Research Institute (PCORI), teaching health centers graduate medical education and Medicaid funding for Puerto Rico and other U.S. territories.

In July, the full House of Representatives passed its FY2020 health spending bill which included a \$2 billion funding increase for NIH. In September, the Senate Labor-Health and Human Services Appropriations subcommittee, chaired by Sen. Blunt (R-MO), which drafts and approves the Senate health spending bill, indefinitely postponed a subcommittee vote on the FY2020 health spending bill, but released the measure to the public. The Senate health spending bill includes a proposed \$3 billion funding increase for NIH. We expect the Senate bill will move forward despite the lack of committee action.

We are cautiously optimistic that NIH is slated for a funding increase of between \$2 - \$3 billion for 2020, but the timeframe for final resolution of FY2020 government spending is unclear. The impeachment process and the President's demand for border wall funding are complicating the spending process and raising the prospects of partisan conflict and a potential government shutdown in December in early in 2020. ■

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^{vi}FDA. FDA Removes 7 Synthetic Flavoring Substances from Food Additives List. CFSAN Constituent Updates 2018 October 5, 2018 [cited 2019 November 20, 2019]; Available from: <https://www.fda.gov/food/cfsan-constituent-updates/fda-removes-7-synthetic-flavoring-substances-food-additives-list>.

^{vii}Allen, JG, et al., Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes. *Environ Health Perspect*, 2016. 124(6): p. 733-9.

^{viii}Tokle, R and W Pedersen, "Cloud chasers" and "substitutes": e-cigarettes, vaping subcultures and vaper identities. *Social Health Illn*, 2019. 41(5): p. 917-932.



ATS 2020

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