PC-FACS

AMERICAN ACADEMY OF HOSPICE AND PALLIATIVE MEDICINE

Feature Editor: Mellar P. Davis, MD, FCCP, FAAHPM

PC-FACS (**F**ast **A**rticle **C**ritical **S**ummaries for Clinicians in **P**alliative **C**are) *provides hospice and palliative care clinicians with concise summaries of the most important findings from more than 100 medical and scientific journals. If you have colleagues who would benefit from receiving PCFACS, please encourage them to join the AAHPM at aahpm.org. Comments from readers are welcomed at pc-facs@aahpm.org.*

Table of Contents

From PC-FACS Issue 199—December 4, 2018

Neuropathic Pain and Opioids: Rojewska E, Wawrzczak-Bargiela A, Szucs E, et al. Alterations in the activity of spinal and thalamic opioid systems in a mice neuropathic pain model. *Neuroscience.* 2018;390:293-302.

Medical Decision Making: Petrillo LA, McMahan RD, Tang V, Dohan D, Sudore RL. Older adult and surrogate perspectives on serious, difficult, and important medical decisions. *J Am Geriatr Soc.* 2018;66(8):1515-1523.

Hospice Utilization in Nursing Homes: Rodriquez J, Boerner K. Social and organizational practices that influence hospice utilization in nursing homes. *J Aging Stud.* 2018;46:76-81.

Nomogram for Advanced Lung Cancer Prognosis: Yap W, Shih M, Kuo C, et al. Development and validation of a nomogram for assessing survival in patients with metastatic lung cancer referred for radiotherapy for bone metastases. *JAMA Netw Open.* 2018;1(6):e183242.

Modes of Pediatric In-Hospital Death: Trowbridge A, Walter JK, McConathey E, Morrison W, Feudtner C. Modes of death within a children's hospital. *Pediatrics.* 2018;142(4). pii: e20174182.

Effect of Antidepressants on Seizures: Finkelstein Y, Macdonald EM4, Li P, Mamdani MM, Gomes T, Juurlink DN. Second-generation anti-depressants and risk of new-onset seizures in the elderly [published online ahead of print July 10]. *Clin Toxicol (Phila).* 2018:1-6. https://doi.org/10.1080/15563650.2018.1483025.

Summaries With Commentaries

Analyzing Alterations in the Activity of Spinal and Thalamic Opioid Systems in a Neuropathic Pain Model

Background. Neuropathic pain typically is less opioid responsive than nociceptive pain.[1-4] What neuropathic pain–related endogenous opioid system changes occur after sciatic nerve chronic constriction injury (snCCI)?

Design and Participants. This study analyzed changes in pain-related behavior in mice 1, 14, and 28 days post-snCCI to determine neuropathic pain–related endogenous opioid system changes. μ-(MOP), δ-(DOP), and κ-(KOP) opioid receptor changes and proenkephalin and prodynorphin mRNA levels as well as GTPγS binding of opioid receptors on the ipsi- and contralateral spinal cord and thalamus were studied 14 days post-snCCI (when pain-related behavior is most observed). Mechanical and thermal stimuli-induced pain thresholds were measured via von Frey and cold-plate tests. ANOVA with Bonferroni's multiple comparison test, non-linear regression, and t-tests were used.

Results. All mice developed tactile/thermal hypersensitivity post-snCCI. Compared to naive mice, no contralateral-paw mechanical/thermal stimuli response changes occurred, but ipsilateral response times were reduced day 1 through 28 (the lowest threshold occurred day 14; all $P<0.001$). Spinal MOP/DOP/KOP mRNA only changed (decreased) on the ipsilateral side; thalamus MOP/DOP/KOP contralateral-side mRNA was reduced, but only MOP mRNA decreased on the ipsilateral side (all $P<0.05$). No contralateral-side spinal prodynorphin/proenkephalin mRNA changes occurred, but ipsilateral-side spinal levels for prodynorphin/proenkephalin mRNA were elevated

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https://doi.org/10.1016/j.jpainsymman.2018.12.005

($P<0.05$). Prodynorphin/proenkephalin thalamus mRNA levels were unaltered. Ipsilateral-side spinal GTPγS binding of MOP/DOP/KOP ligands decreased (all $P<0.01$), yet the effect was smaller for DOP ligands (possibly indicating weaker ascending nociceptive pathway stimulation); a contralateral-side decrease occurred for all thalamus opioid receptor (especially DOP) ligands (all $P<0.05$). Thus, drugs with higher DOP affinity may improve neuropathic pain treatment.

Commentary. Opioid receptors "hide" when it comes to neuropathic injury. The mechanism is either by methylation of receptor promoter sites; deacetylation of histones, which prevents DNA unwinding; or production of certain micro RNAs, which silence mRNA and thus prevent protein receptor production. The initial focus by basic science researchers has been on mu receptors, and the authors now extend this observation to include kappa and delta opioid receptors. Delta receptors were less influenced by injury. What this tells us is that there is a global reduction in opioid receptors and compensatory increase in endogenous ligands. Opioids like nalbuphine, a kappa agonist, may not be superior to morphine as analgesics for neuropathic pain, theoretically. The way forward is to reverse the epigenetic receptor modulating responses to nerve injury and target nonopioid pathways first. It is instructive that pregabalin has been found superior to fentanyl when treating cancer-related neuropathic pain.[5]

Bottom Line. Opioid receptors, including kappa and delta receptors, are downmodulated upstream of neuropathic injury, leading to hypersensitivity.

Reviewer. Mellar P. Davis, MD FCCP FAAHPM, Geisinger Medical Center, Pittsburgh, PA.

Source. Rojewska E, Wawrzczak-Bargiela A, Szucs E, et al. Alterations in the activity of spinal and thalamic opioid systems in a mice neuropathic pain model. *Neuroscience.* 2018;390:293-302.

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Older Adult and Surrogate Perspectives on the Medical Decision-Making Process

Background. Clinicians can promote patient centeredness (aligning care to individuals' values/preferences) by supporting patients and surrogates in the shared decision-making process.[1,2] What helps racially and ethnically diverse older adults and their surrogates make serious decisions?

Design and Participants. This study explored medical decisions that diverse older adults and surrogates perceive as serious, difficult, and important and what helped them make those decisions. A convenience sample was recruited from clinics, support groups, and senior centers, and 13 focus groups were conducted at 3 urban hospitals 2010-2011. Participants were eligible if they were age ≥65 years and had made a serious medical decision for themselves or were age ≥18 years and had made a serious medical decision for another. Participants were asked to describe decisions they had made (eg, emergency surgery, chemotherapy, and life-prolonging procedures). The constant comparative method refined the coding scheme, and focus groups were conducted until reaching thematic saturation.

Results. Patients (mean age 78 years [range 64-89]) and surrogates (57 years [33-76]) were 48% female, 29% African American, 26% white, 26% Asian or Pacific Islander, and 19% Hispanic (N=69). In the study, 168 decisions were identified (59% as older adults, 41% as surrogates). Older adults from all racial and ethnic groups frequently recalled decisions about cancer treatment and chronic illness management. Surrogates described decisions about transitions in care (eg, acute care to hospice) and medical crises. Values and information sources helped participants make decisions. Older adults valued self-sufficiency and maximizing survival and relied on personal experiences as often as medical advice. In all racial/ethnic groups, surrogates valued avoiding suffering for loved ones.

Commentary. How do surrogates and older adult patients approach decision making in the case of serious medical illness? By analyzing focus group conversations, the authors were able to identify the more

common themes involved in decision making, including patient and surrogate values (self-sufficiency, survival, religion, avoidance of suffering) and reliance on a variety of information sources (doctors, personal experience, personal research). A key strength of this study was the ethnic and racial diversity of the participants. There was some minor variation between patients and surrogates in how much decisional weight was placed on different themes, though in general there was agreement on the values important to decision making.

Bottom Line. Ethnically and racially diverse surrogates and older adult patients may vary in their use of informational sources and personal values in medical decision making, but overall there are more similarities than differences.

Reviewer. Erin Zahradnik, MD, University of Chicago, Chicago, IL.

Source. Petrillo LA, McMahan RD, Tang V, Dohan D, Sudore RL. Older adult and surrogate perspectives on serious, difficult, and important medical decisions. *J Am Geriatr Soc.* 2018;66(8):1515-1523.

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Influence of Social Practices and Beliefs on Hospice Utilization in Nursing Homes

Background. Currently, 1.8 million individuals reside in nursing homes, most of whom for long-term care.[1] How do nursing home staff beliefs and work routines influence hospice utilization?

Design and Participants. This qualitative study analyzed how staff beliefs and work routines influence hospice utilization in 2 Massachusetts nursing homes. Staff members who had a role in hospice utilization were interviewed (30-60 minutes; January-May 2017). Questions and specific issues discussed varied depending on who was being interviewed and their position. Staff were asked to describe their experiences, including interactions about hospice with residents, family members, and colleagues, and share any perceived challenges. Interviews were audio-recorded and transcribed, and a coding system was developed with an analytical theme-identification approach. Hospice utilization was measured as the ratio of the number of deaths on hospice to total deaths.

Results. Twenty-one staff members were interviewed: 10 (Site 1) and 11 (Site 2). One had a higher proportion of long-term care residents, while 2 had a higher proportion of post-acute care residents. Seventy-six percent of residents died on hospice at 1 and 24% at 2. Staff-identified barriers to hospice included families who saw hospice as giving up and gaps in the reimbursement system. At 1, staff said hospice care extended beyond what they provided on their own. At 2, an influential group said hospice was essentially the same as their own end-of-life care, and therefore unnecessary. Staff at 1 proactively approached families about hospice, whereas staff at 2 took a reactive approach, getting hospice when families asked for it.

Commentary. Hospice utilization varies significantly between nursing homes, as does the quality of end-of-life care provided. There is debate on how much value hospice adds in nursing homes, particularly in facilities that already provide high-quality end-of-life care. Patients with complex symptom burden or with highly distressed families might be more likely to benefit from hospice than patients without complex needs. Although this study doesn't answer the question of how to ensure good end-of-life care in nursing homes, it does provide some insights into factors impacting hospice utilization. To improve end-of-life care, multiple factors, including restructuring the way Medicare pays for end-of-life-care in nursing homes, will likely need to be addressed.

Bottom Line. Nursing home leadership and staff members' attitudes toward hospice significantly impact hospice utilization rates among nursing home residents and should be considered a potentially modifiable factor to improve end-of-life care in nursing homes.

Reviewer. Bree Johnston, MD MPH, University of Arizona College of Medicine, Tucson, AZ.

Source. Rodriquez J, Boerner K. Social and organizational practices that influence hospice utilization in nursing homes. *J Aging Stud.* 2018;46:76-81.

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1. Ersek M, Carpenter JG. Geriatric palliative care in long-term care settings with a focus on nursing homes. *J Palliat Med.* 2013;16(10):1180-1187.

Examining a New Model for Prognostication in Patients with Bone Metastases from Lung Cancer

Background. Most patients who develop bone metastases from lung cancer (LC) will receive radiotherapy.[1,2] Can a newly developed model for patients

receiving radiotherapy for LC-derived bone metastases improve survival prediction?

Design and Participants. This study developed and validated a nomogram for assessing survival probability among patients with metastatic LC receiving radiotherapy for osseous metastases. Data from patients at a northern Taiwan tertiary medical center (2000-2013) were used to develop the nomogram. A cohort of similar patients at a southern Taiwan tertiary medical center (2011-2017) composed the external validating set. Analysis included multivariable Cox regression.

Results. Training-set patients (n=477) were 61% male and mean (SD) age 63 (12) years. Validating-set patients (n=235) were 48% male and age 63 (12) years. In the training set, 39%, 61%, and 75% died within 3, 6, and 12 months (median survival=4.21, 95% CI=3.68-4.9). In the validating set, 36%, 51%, and 61% died within 3, 6, and 12 months (5.20, 4.07-7.17). Body mass index (BMI; 19-<25 vs. ≥25: hazard ratio=1.42, 95% CI=1.14-1.78; <19 vs. ≥25: 2.31, 1.56-3.44), histology (non-small cell vs. small cell LC: 0.59, 0.41-0.86), epidermal growth factor receptor (EGFR) mutation (positive vs. unknown: 0.66, 0.46-0.93; negative vs. unknown: 0.98, 0.66-1.45), smoking status (ever-smoker vs. never-smoker: 1.50, 1.24-1.83), age, and neutrophil-to-lymphocyte ratio were incorporated. The age and neutrophil-to-lymphocyte ratio hazard ratios were modeled nonlinearly with restricted cubic splines ($P<.001$). The nomogram's discriminative ability was good in the training set (C statistic, ≥0.77; $P<.001$) and was validated with internal (bootstrap; ≥0.76; $P<.001$) and external validation (≥0.75; $P<.001$).

Commentary. In the era of expanded treatment options, patients with advanced lung cancer deserve more precise prognostication than general tools, such as the Palliative Prognostic Index, can provide. Without better tools, clinicians tend to overestimate lung cancer patients' prognosis.[3] The nomogram could be used by oncologists, radiation oncologists, and palliative care clinicians. The study used six variables, all objective and readily available to providers. Not surprisingly, histology, smoking, age, and EGFR mutation correlated to prognosis. BMI and neutrophil-to-lymphocyte ratio (representative of cancer-related cachexia and systemic inflammation, respectively) were more prognostically significant than subjectively measured performance status in the combined analysis. The tool was developed and externally validated within Taiwan; continued validation should be pursued to determine its generalizability for a heterogeneous population.

Bottom Line. The nomogram, available as a web-based tool (http://178.128.122.192:81/Lung-boneMet/), provides prognostic information for advanced lung cancer patients, which may be helpful in guiding treatment plans and advance care planning conversations.

Reviewer. Laura R. Hallstrom, MD, and Renato V. Samala, MD HMDC FACP FAAHPM, Cleveland Clinic, Cleveland, OH.

Source. Yap W, Shih M, Kuo C, et al. Development and validation of a nomogram for assessing survival in patients with metastatic lung cancer referred for radiotherapy for bone metastases. *JAMA Netw Open.* 2018;1(6):e183242.

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Characteristics Associated with Modes of Pediatric In-Hospital Death

Background. Most of the 45,000 American infants, children, and adolescents who die annually do so in hospitals.[1,2] What are the modes of pediatric patient in-hospital death, and are patient or clinical care characteristics associated with mode of death (MOD)?

Design and Participants. This retrospective cross-sectional study distinguished MODs among children who died in a major tertiary care children's hospital 2011-2014, then determined if patient or clinical care characteristics were associated with MOD. Exclusions: stillborn infants, infants who were born at a previable age, and patients who died immediately after emergency department arrival. A review of provider notes and resuscitation records enabled creation of 5 MODs: withdrawal of life-sustaining technologies (WLST), nonescalation (no resuscitation attempt), failed resuscitation (code), code-then-withdrawal, and neurologic criteria death. Descriptive statistics, $\chi 2$ tests, and multinomial logistic regression were used.

Results. Patients (n=579) were 61% age <1 year, 50% male, and 39% white. The most common death locations were neonatal intensive care unit (ICU; 30%), pediatric ICU (28%), and cardiac ICU (17%). The most common MODs were WLST (40%), nonescalation (26%), failed resuscitation (23%), code-then-withdrawal (6%), and neurologic criteria (5.3%). Patients were more likely to receive palliative

care consultation (PCC) if they were in the oldest age group (odds ratio=9.5; 95% CI=2.72-33.5) or had a neonatal complex chronic condition (2; 1.05-3.8) or malignancy (12; 5.53-26.1). Patients who received PCC were less likely to experience a code death (0.31; 0.13-0.75); however, African American (vs. white) patients were more likely to experience a code death (2.46; 1.05-5.73). Patients who had a nonescalation death were more likely to have had PCC (5.02; 2.77-9.10).

Commentary. Although an increasing number of pediatric patients are dying at home,[3] the majority still die in the hospital. In this study, three-quarters of pediatric hospital deaths occurred in some form of ICU, and two-thirds were preceded by either WLST or nonescalation (such as not attempting resuscitation). PCC was obtained in one-third of the patients who died in the hospital and appeared to influence the family's decision. Patients who received PCC were more likely to have a nonescalation death and less likely to have a code death. Within the first 24 hours of hospitalization, African American patients were much more likely to have a code death compared to white patients, with no difference thereafter. This could reflect distinct priorities, clinician bias, or insufficient advance care planning.

Bottom Line. PCC is associated with reduced likelihood of a code death in children, and additional focus on early hospitalization could conceivably minimize racial disparities.

Reviewer. Sue S. Sreedhar, MD, Critical Care and Palliative Care, Johns Hopkins All Children's Hospital, St. Petersburg, FL.

Source. Trowbridge A, Walter JK, McConathey E, Morrison W, Feudtner C. Modes of death within a children's hospital. *Pediatrics*. 2018;142(4). pii: e20174182.

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Effect of Antidepressants on the Risk of New-Onset Seizures in Elderly Patients

Background. Seizures are a serious but less appreciated consequence of antidepressant therapy.[1] What is the risk of a first seizure among patients receiving the most popular antidepressants?

Design and Participants. This population-based, case-control study ranked the seizure risk of popular antidepressants. Ontario, Canada residents age ≥65 years who were hospitalized for a first-ever seizure within 60 days of filling a prescription for 1 of 9 second-generation antidepressants were included. The most commonly prescribed antidepressants in Ontario were identified, each dispensed more than 1 million times (range=1,196,810 [fluvoxamine]-19,849,930 [citalopram]; 2002-2015): citalopram, venlafaxine, paroxetine, sertraline, escitalopram, fluoxetine, duloxetine, fluvoxamine, and bupropion. Bupropion was selected as the reference exposure, as it is known to carry a dose-dependent seizure risk (~20% of patients demonstrate electroencephalographic abnormalities). Exclusions: patients receiving any other antidepressant (cyclic antidepressants and monoamine oxidase inhibitors) and patients with an overdose-induced seizure. For each case, 1-4 seizure-free control subjects were selected, matching on age, sex, and index date; each received 1 study antidepressant in the 60 days preindex date. Conditional logistic regression was used.

Results. In the study, 5,701 patients (median [IQR] age 78 [72-84] years and 39% male) were matched with 21,872 controls. Relative to bupropion, the risk of new-onset seizure during therapeutic use was highest for escitalopram (adjusted odds ratio [AOR]=1.79; 95% CI=1.42-2.25) and citalopram (AOR=1.67; 95% CI=1.35-2.07), followed by sertraline (AOR=1.55; 95% CI=1.23-1.94) and fluvoxamine (AOR=1.52; 95% CI=1.12-2.06), while no incremental risk was found for fluoxetine (AOR=1.02; 95% CI=0.78-1.33) or duloxetine (AOR=0.94; 95% CI=0.75-1.22). Other antidepressants were associated with modest increase in seizure risk.

Commentary. Second-generation antidepressants are considered generally well-tolerated and often are prescribed for palliative care patients. However, the risk of new-onset seizures that can occur at therapeutic doses is largely undepreciated. This large population-based study showed that escitalopram and citalopram were associated with significantly higher risk of seizures in elderly patients than bupropion (a well-known proconvulsant agent). This is important for palliative care clinicians as patients with advanced illness may already be at increased risk for seizures due to not only advanced age but also other medications and disease-related factors. Mirtazapine is the most common antidepressant used in cancer

patients[2-9] (Cipriani and Andrade papers also are helpful references for readers[10,11]).

Bottom Line. Many second-generation antidepressants, in particular escitalopram and citalopram, significantly increase the risk of seizures in elderly patients.

Reviewer. Dulce M. Cruz Oliver, MD CMD FAAHPM AGSF, The Johns Hopkins Hospital, Baltimore, MD.

Source. Finkelstein Y, Macdonald EM4, Li P, Mamdani MM, Gomes T, Juurlink DN. Second-generation anti-depressants and risk of new-onset seizures in the elderly [published online ahead of print July 10]. *Clin Toxicol (Phila).* 2018:1-6. doi: 10.1080/15563650.2018.1483025.

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Rave Reviews

Cain CL, Surbone A, Elk R, Kagawa-Singer M. Culture and palliative care: preferences, communication, meaning, and mutual decision making. J Pain Symptom Manage. 2018;55(5):1408-1419.

This review article, part of a special series on diversity in *JPSM*, highlights the significant ways in which culture influences palliative care. Examples are provided of how and why varied responses to pain and suffering occur in different ways, focusing on four areas of palliative care: care preferences, communication patterns, different meanings of suffering, and the decision-making process about care. Recommendations are made to assist clinicians in providing culturally based, high-quality palliative care for all patients.

Niknejad B, Bolier R, Henderson CR Jr, et al. Association between psychological interventions and chronic pain outcomes in older adults: a systematic review and meta-analysis. JAMA Intern Med. 2018;178(6):830-839.

Chronic noncancer pain is common among older adults and usually managed with pharmacotherapies that often are unhelpful in alleviating symptoms. In the wake of the opioid epidemic, other strategies are being examined. This systematic review and meta-analysis examined the efficacy of psychological interventions in older adults with such pain. They found that psychological interventions have a small but beneficial effect on the short-term management of pain, catastrophizing, and self-efficacy in managing pain. These benefits were strongest when using group-based interventions. Results were inconsistent across patients though, with some experiencing substantial alleviation of symptoms and others none.

O'Donnell AE, Schaefer KG, Stevenson LW, et al. Social worker—aided palliative care intervention in high-risk patients with heart failure (SWAP-HF): a -pilotrandomized clinical trial. JAMA Cardiol. 2018;3(6):516-519.

A goal of care intervention (conversation with palliative care trained social workers) was examined among patients with heart failure in a randomized control trial. This intervention, that began in the hospital and continued in an outpatient setting, enhanced prognostic understanding and patient-physician communication about goals of care without negatively impacting quality of life.

PC-FACS Feedback

We appreciate your feedback. Help us help you—send your comments to pc-facs@aahpm.org.

PC-FACS was created in 2005 by Founding Editor-in-Chief *Amy P. Abernethy, MD, PhD, FACP, FAAHPM.* The Academy is deeply grateful to Dr. Abernethy for creating this important publication and for her many contributions to the field of hospice and palliative medicine.

PC-FACS is edited by Editor-in-Chief, *Mellar P. Davis, MD, FCCP, FAAHPM*, of the Geisinger Health System, and Associate Editor-in-Chief, *Robert M. Arnold, MD, FAAHPM*, of the University of Pittsburgh Medical Center. All critical summaries are written by *Jeff Fortin, MD. AAHPM* thanks the following PC-FACS Editorial Board members for their review of the critical summaries and preparation of the commentaries:

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