PC-FACS

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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 pcfacs@aahpm.org.*

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Summaries With Commentaries

Coadministering Gabapentenoids to Avoid Opioid-Induced Hyperalgesia and Analgesic Tolerance in Rats

Background. Prolonged opioid use can cause hyperalgesia and analgesic inefficacy.[1-3] Do α2δ-1-bound N-methyl-D-aspartate receptors (NMDARs) contribute to presynaptic NMDAR hyperactivity associated with opioid-induced hyperalgesia and analgesic tolerance?

Design and Participants. This study tested whether α2δ-1-bound NMDARs contribute to presynaptic NMDAR hyperactivity associated with opioid-induced

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hyperalgesia and analgesic tolerance. Rats (5 mg/kg) and wild-type and α2δ-1-knockout mice (10 mg/kg) were treated intraperitoneally with morphine twice/day for 8 days, and nociceptive thresholds were examined. Presynaptic NMDAR activity was recorded in spinal cord slices, and coimmunoprecipitation examined protein-protein interactions. The Kolmogorov-Smirnov test, t-tests, and one- and two-way ANOVAs with Tukey's test were used.

Results. Morphine in rats increased α2δ-1 protein in the dorsal root ganglion (P=0.039, $t_{(10)}$=2.37, n=6 rats/group) and spinal cord (P=0.014, $t_{(10)}$=2.97; n=6 rats/group) and increased the physical interaction between α2δ-1 and NMDARs by $1.5^{+/-}0.3$ fold (means$^{+/-}$SD, P=0.009, n=6 rats/group; P=0.009, $t_{(10)}$=3.213, n=6 rats/group) and the prevalence of α2δ-1-bound NMDARs at spinal cord synapses (P<0.001, $t_{(10)}$=9.285, n=6 rats/group). Inhibiting α2δ-1 with gabapentin ($4.44^{+/-}1.29$ Hz vs. $6.74^{+/-}1.09$ Hz, P<0.001, $F_{(5,57)}$=11, n=10 neurons) or α2δ-1 genetic knockout ($449^{+/-}87$ pA vs. $368^{+/-}61$ pA, P=0.04, $F_{(5,60)}$=5.58) abolished the morphine-induced spinal dorsal horn increase in presynaptic NMDAR activity. Uncoupling the α2δ-1-NMDAR interaction with an α2δ-1 C terminus-interfering peptide reversed morphine-induced tonic activation of NMDARs at the central terminal of primary afferents ($503^{+/-}34$ pA vs. $394^{+/-}52$ pA, P<0.001, $F_{(5,60)}$=16). Finally, either gabapentin (n=8) or an α2δ-1 C terminus-interfering peptide (n=10) blocked the morphine-induced mechanical/thermal hyperalgesia and attenuated the morphine-induced analgesia reduction. In knockouts, morphine did not affect baseline withdrawal threshold, and 8-day morphine-induced antinociception was preserved (n=8; all P<0.05).

Commentary. The molecular pathophysiology underlying opioid-induced hyperalgesia and tolerance remains a mystery. This study highlights that the binding of protein α2δ-1 with NMDARs is essential to the development of opioid-induced hyperalgesia and tolerance.

The findings suggest that coadministration of opioids and gabapentenoids, which selectively target protein α2δ-1 binding to NMDARs, may be a better approach then using a complete NMDA antagonist like ketamine[4] to prevent opioid-induced hyperalgesia and tolerance. In clinical practice, patients who develop hyperalgesia or tolerance with chronic use of opioids may be rotated, with restoration of antinociception.[5] In patients who have multiple opioid allergies where an opioid rotation may be problematic, the addition of gabapentin may be an alternative option if clinical trials confirm the findings of the study.

Bottom Line. In rats, binding of α2δ-1 protein subunit to NMDARs is implicated in the development of opioid-induced hyperalgesia and tolerance, which can be reversed by gabapentinoids.

Reviewer. Regina M. Mackey, MD, Center for Palliative Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, MN

Source. Deng M, Chen SR, Chen H, Pan HL. α2δ-1−Bound N-methyl-D-aspartate receptors mediate morphine induced hyperalgesia and analgesic tolerance by potentiating glutamatergic input in rodents. *Anesthesiology.* 2019;130(5):804-819.

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Finding Hope and Healing When Cure Is Not Possible

Background. Traditional medical training may underprepare clinicians to provide comfort to patients facing life-limiting illness and their families.[1,2] How can clinicians facilitate emotional healing in pediatric patients with brain cancer and their families?

Design and Participants. This article explored the evolution of hope for pediatric patients with brain cancer and their families during the course of incurable illness and examined how clinicians can help guide the emotional healing process.

Results. Clinicians can help families transition from "focused hope" (cure/remission-focused) to "intrinsic hope" (a more present-focused, profound, and resilient emotional foundation) as death approaches and letting go becomes essential. As their expectations of cure diminish, parents report gradual increases in hope regarding their child's quality of life and the awareness of the broader

meaning of hope. Focused hope can degenerate into the use of ineffective/uncomfortable treatments and, when maintained until death, often produces posttraumatic stress and depression. Clinicians can give parents time "out of the fight" to create special moments to reflect and inquire about patients'/parents' concerns (listening for underlying feelings and asking questions to bring them out). Once trust is established, clinicians may help reframe unrealistic expectations. Parents/patients should never hear "nothing more can be done"; when treatment stops, hospice and palliative medicine provide care aimed at physical, emotional, and spiritual comfort. Unconditional presence (accepting any outcome their patients experience without judging it as good/bad) keeps clinicians connected with patients during the worst of times. Handling despair properly (as multilayered challenges that might be resolved individually) without avoidance is critical. Formulating concrete goals of care that include end-of-life plans can relieve parents' distress.

Commentary. Hope can be both the palliative clinician's best friend or, in unrealistic settings, our worst nightmare. This article is an anecdotal, experiential story that helps us take pause and reflect on the meaning of hope. The authors examine the evolution of hope and apply strategic teaching points to one of the most emotionally difficult areas in medicine: children with brain tumors. The authors do for hope what Kubler-Ross did for grief. By explaining focused versus intrinsic hope, they provide guidance for when parents may be open to information and how they are likely to respond to it. This allows the caregiver to approach parents in a caring and realistic fashion that is not likely to be received negatively.

Bottom Line. For clinicians struggling with families locked in unrealistic expectation, counting on providence, this guide can help them deal with issues of hope, miracles, and the way forward.

Reviewer. Greg Phelps, MD MPH MAHCAM FAAHPM, Hospice of Chattanooga, UT College of Medicine, Chattanooga, TN

Source. Stuart B, Danaher T, Awdish R, Berry L. Finding hope and healing when cure is not possible. *Mayo Clin Proc.* 2019;94(4):677-685.

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Racial/Ethnic Differences in Prognosis Communication Among Patients with Advanced Cancer

Background. Healthcare disparities are particularly prevalent in end-of-life (EOL) care.[1] Does prognosis communication (PCom) during inpatient palliative care (PC) conversations differ for African American or Latino patients with advanced cancer compared to white patients?

Design and Participants. This study at 2 academic medical centers examined whether conversations involving African American or Latino patients with advanced cancer compared with white patients differ in terms of PCom. The data derive from a cohort study of inpatient PC consultations among patients with advanced cancer.[2] Initial consultations between PC clinicians and hospitalized patients (aged >21 years) were audio-recorded. Blinded researchers coded for the presence and characteristics of PCom (any prediction or anticipatory guidance about future course of illness). Patients' and family's requests for prognosis were not included, nor clinicians' questions about how much prognostic information the patient desired. Chi-square, t-tests, multiple logistic regression, and Wilcoxon rank-sum and Fisher's tests were used.

Results. Patients (n=231) were 21% African American or Latino, 50% female, 29% aged <55 years, and 62% financially insecure. Patients' cancers were 22% lung and 18% gastrointestinal (noncolorectal). African Americans or Latinos were younger, more financially insecure, and less educated ($P<.05$). Clinicians were 4% African American or Latino and 53% female. Twenty-five were attending physicians, 16 were PC physician fellows, and 6 were nurse practitioners. Thirty-four percent had practiced PC >5 years. Seventy-six percent of consultations contained PCom, which was more common among patients who self-identified as neither African American nor Latino (ORadj=2.11; 95% CI=1.04-4.29). When PCom occurred, optimistically cued information ("good news") was more common among patients who self-identified as neither African American nor Latino (ORadj=8.82; 1.16-67.18). Other PCom characteristics did not differ.

Commentary. Ethnic/racial minorities in the United States are less likely to receive preference-concordant EOL care.[3,4] Inadequate communication by PC clinicians about prognosis may play a role. This study found that at the initial consultation, PC clinicians communicated PCom less frequently to African American/Latino patients compared to white patients and delivered more optimistically cued PCom to white patients compared to African American/Latino patients. Possible explanations for this are suggested, but future research is needed.

Bottom Line. This study raises potential concerns about how PC clinicians communicate with minority

patients about prognosis. This may represent a missed opportunity to reduce ethnic disparities in preference-discordant EOL treatment.

Reviewer. Mei-Ean Yeow, BMBCh FACP FAAHPM, Center for Palliative Medicine, Mayo Clinic, Rochester, MN

Source. Ingersoll LT, Alexander SC, Priest J, et al. Racial/ethnic differences in prognosis communication during initial inpatient palliative care consultations among people with advanced cancer [published online ahead of print January 2, 2019]. *Patient Educ Couns.* pii: S0738-3991(18)30694-3. https://doi.org/10.1016/j.pec.2019.01.002.

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Association of Expanded VA Hospice Care With Aggressive Care and Cost

Background. The Comprehensive End-of-Life (EOL) Care Initiative improved veterans' hospice access.[1] Does increased veterans' hospice availability reduce EOL intensive treatments (ITs) and medical costs?

Design and Participants. This study investigated whether allowing veterans to access cancer treatment concurrently with hospice is associated with a change in end-of-life care and healthcare costs. Patient outcomes during years with relatively high vs. lower hospice use were compared. Veterans newly diagnosed with stage IV non-small cell lung cancer (NSCLC; 2006-2012) from Veterans Affairs (VA) Medical Centers (VAMCs) with ≥5 stage-IV NSCLC-diagnosed veterans/year were evaluated. VA inpatient, outpatient, pharmacy claims, and similar Medicare data were used to create VAMC-level annual aggregates of all patients who died of cancer with hospice use, cancer treatment, and/or concurrent receipt of both in the last month of life, dividing all VAMC years into quintiles of exposure to hospice availability. Outcomes: ITs (≥2 hospital admissions ≤30 days, tube feeding, mechanical ventilation, intensive care unit [ICU] admission) and total costs ≤6 months postdiagnosis. Logistic regression and ordinary least squares were used.

Results. Veterans (n=13,085) were 98% male, 81% white, and 46% aged >65 years. Veterans treated in a VAMC in the top hospice quintile (79% hospice users), relative to the bottom quintile (55%), were >2 times more likely to have concurrent cancer treatment after initiating hospice (adjusted odds ratio [AOR]=2.28; 95% CI=1.67-3.31). For veterans seen in top (relative to bottom) hospice quintile VAMCs, the AOR of receiving IT was 0.66 (CI=0.53-0.81) and the AOR of ICU use was 0.78 (CI=0.62-0.99). Six-month costs were ~$266/day lower (CI=−$358−−$164) for the high-quintile vs. low-quintile group. Survival did not differ.

Commentary. Since 2009, the VA has allowed veterans to receive hospice and disease-modifying treatments concurrently since 2009. This is the first large-scale analysis of the association of VA concurrent care with costs. Authors conducted a retrospective difference-in-differences analysis at the level of VAMCs to avoid selection bias inherent in comparisons of individuals who do or do not elect hospice. After controlling for prior healthcare utilization, VA benefits, and comorbidities, veterans treated in VAMCs in the top quintile of hospice utilization were more likely to receive concurrent hospice and chemotherapy/radiation. Moreover, these same veterans were less likely to receive ICU care, mechanical ventilation, or feeding tubes. Cost savings were driven primarily by reduction in inpatient care. Whether cost-savings are reproducible outside the VA remains to be seen, but this study convincingly demonstrates that chemotherapy or radiation concurrent with hospice is not associated with an increase in other aggressive care.

Bottom Line. Increased hospice for veterans with lung cancer, with access to concurrent anticancer treatments, is associated with lower aggressive care and EOL costs.

Reviewer. Nina O'Connor, MD FAAHPM, University of Pennsylvania, Philadelphia, PA

Source. Mor V, Wagner TH, Levy C, et al. Association of expanded VA hospice care with aggressive care and cost for veterans with advanced lung cancer [published online ahead of print on March 28, 2019]. *JAMA Oncol.* https://doi.org/10.1001/jamaoncol.2019.0081.

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Outcomes of Extremely Preterm Infants With Birth Weight Less Than 400g

Background. At extremely early gestational ages (GAs), birth weight (BW) may influence decisions regarding resuscitation initiation.[1-3] What are the mortality and morbidity risks for infants at BW<400g?

Design and Participants. This 21-center, retrospective study reported in-hospital and 2-year outcomes of a cohort of preterm infants (GA=22-26 weeks) who were born at BW<400g (2008-2016) without major birth defects. The primary outcome was survival to discharge among active treatment-receiving infants. Active treatment (AT) was any potentially lifesaving intervention at birth. Follow-up data included 2008-2015 births, ensuring children had reached 18-26 months' corrected age. Neurodevelopmental impairment was defined as a Bayley-III[4] cognitive composite score <85, motor composite score <85, moderate/severe cerebral palsy, gross motor function classification system score ≥2, bilateral blindness, and/or hearing impairment. $\chi 2$, Fisher's test, univariate logistic regression, descriptive statistics, exact confidence intervals, and the Kaplan-Meier method were used.

Results. Infants (n=205) were 59% female, 65% singletons, and 87% small for GA. Thirteen percent (95% CI=8.5-19) overall survived to discharge. Sixty-three percent were born at 22-23 weeks' GA, and 49% received AT. AT increased with GA (15% at 22 weeks' GA; 94% at 26 weeks' GA; $P<.001$) and raised antenatal steroid ($P<.001$) and antenatal antibiotic ($P=.01$) exposure likelihoods. With AT, survival to discharge increased with advancing GA, from 17% (CI=6.4-33) at 22-23 weeks' GA to 32% (CI=18-50) at 25-26 weeks' GA ($P<.001$). Of those not receiving AT, 99% died ≤12 hours after birth. Among AT infants born 2008-2015, 26% (CI=17-36) survived to discharge and 21% (CI=13-31) were evaluated at follow-up (74% of whom incurred moderate/severe neurodevelopmental impairment).

Commentary. The threshold of viability seems to be getting lower every day. Less than a decade ago, the Neonatal Resuscitation Program recommended that resuscitation be withheld for any newborn weighing <400g.[5] However, this study reveals that 1-out-of-4 of these neonates will survive with AT. Yet, while it would be inaccurate to say that such micropreemies have "no chance," morbidity remains extremely high. Three out of 4 survivors had at least moderate neurologic disability and the majority were rehospitalized within the first 2 years of life. This study underscores the importance of joint decision making and individualized care plans for the most ill premature babies.

Bottom Line. Infants weighing <400g remain at very high risk of dying or developing severe comorbidities despite contemporary high-intensity interventions.

Reviewer. Regina Okhuysen-Cawley MD, Baylor College of Medicine, Houston, TX

Source. Brumbaugh JE, Hansen NI, Bell EF, et al. Outcomes of extremely preterm infants with birth weight less than 400g [published online ahead of print on March 25, 2019]. *JAMA Pediatr.* https://doi.org/10.1001/jamapediatrics.2019.0180.

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Patient-Centered Decisions About Serious Illness Care

Background. "High-quality medical decisions" reflect choices that are medically feasible and intended to promote patients' values.[1] What is the best approach to patient-centered decisions about serious illness care?

Effects of a Personalized Web-Based Decision Aid for Surrogate Decision Makers

Design and Participants. This multicenter, randomized controlled trial examined whether a decision aid about prolonged mechanical ventilation improved clinician-surrogate concordance on 1-year survival estimates. A web-based decision aid provided personalized prognostic

estimates, explained treatment options, and interactively clarified patient values to inform a family meeting. Secondary outcomes: (1) surrogates' psychological distress, decisional conflict, and communication quality and (2) patients' length of stay and 6-month mortality.

Results. Participants were adult patients (n=277) receiving prolonged mechanical ventilation and their surrogates (n=416) and clinicians (n=427). Neither between-group concordance nor surrogates' estimates of patients' 1-year prognoses differed postintervention; surrogate prognoses (median, intervention=86% vs. control=93%) were more optimistic than a validated prediction model (intervention=57% vs. control=54%). Forty-three percent of intervention surrogates favored more aggressive treatment than their report of patient preferences. Although intervention surrogates had greater reduction in decisional conflict than control surrogates (P=0.041), other surrogate and patient outcomes did not differ.

Intuitive vs. Deliberative Approaches to Making Decisions About Life Support

Design and Participants. This trial, in an urban academic hospital, attempted to identify differences in patients' decisions about life support interventions and goals of care when made intuitively vs. deliberatively. Patients with serious illnesses were asked to express treatment preferences in multiple hypothetical scenarios. The intuitive group was subjected to a cognitive load and instructed to answer questions immediately. The deliberative group was not cognitively loaded and was instructed to think carefully before answering.

Results. Patients were 66% male and mean (SD) age 67 (5) years. Similar proportions of intuitive (n=97) and deliberative (n=102) patients would accept a feeding tube for chronic aspiration (42% vs. 44%), antibiotics for life-threatening infection (39% vs. 43%), mechanical ventilation (59% vs. 60%), and tracheostomy (37% vs. 41%). Deliberative patients were more likely to choose a palliative treatment approach (45% vs. 30%; P=.04). Across scenarios, between-group decisional uncertainty was similar, and intuitive decisions were equally or more closely aligned with patients' health state valuations.

Commentary. The findings of these well-designed, methodologically rigorous studies point to the complexity of decision-making processes about end-of-life care for both patients and their surrogates. Findings from the first study indicate that providing personalized information to surrogate decision makers of critically ill patients is unlikely to temper their overly optimistic estimates of the patient's prognosis or change their decisions about goals of treatment. However, it may reduce their decisional conflict, which is arguably an important outcome. The authors note that the lack of intervention effects may be because of a mismatch between the highly emotional nature of the clinical context (eg, surrogates faced with making end-of-life decisions for a loved one with a critical illness of sudden onset and rapid pace) and a decision aid that focused largely on cognitive rather than emotional aspects of decision making. Findings from the second study, conducted in a less emotionally charged clinical context (eg, hospitalized patients making hypothetical decisions), also suggest that interventions encouraging more thoughtful deliberation about decisions of care are unlikely to improve patients' decision-making processes, including making more value-concordant decisions. Taken together, these studies raise important questions regarding how best to support patients and family members in making decisions consistent with their values.

Bottom Line. The development of effective interventions for facilitating patient-centered decisions about serious illness care need to address both cognitive and emotional factors important to decision-making processes and be tailored to the clinical context in which decisions are being made.

Reviewer. Laura Porter, PhD, Duke University Medical Center, Durham, NC

Sources. Cox CE, White DB, Hough CL, et al. Effects of a personalized web-based decision aid for surrogate decision makers of patients with prolonged mechanical ventilation: a randomized clinical trial [published online ahead of print January 29, 2019]. *Ann Intern Med.* https://doi.org/10.7326/M18-2335.

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Effect of Doxepin Mouthwash or Diphenhydramine-Lidocaine-Antacid Mouthwash vs. Placebo on Radiotherapy-Related Oral Mucositis Pain

Background. Radiotherapy- and chemoradiotherapy-induced oral mucositis is a substantial adverse effect of head and neck cancer treatment.[1] Can doxepin mouthwash or diphenhydramine-lidocaine antacid mouthwash treat oral mucositis-related pain?

Design and Participants. This double-blind trial evaluated whether doxepin mouthwash or diphenhydramine-lidocaine-antacid mouthwash reduces oral mucositis-related pain in patients undergoing oral

radiotherapy for head and neck cancer. Patients had an Eastern Cooperative Oncology Group performance status of 0-2, and oral mucositis pain rated ≥4. Total oral mucositis pain reduction (defined by the area under the curve and adjusted for baseline score) was measured 4 hours after 1 dose (minimal clinically important difference=3.5 points). All scales=0-10 (best-worst). Linear mixed modeling, Wilcoxon rank-sum tests, $\chi 2$, Hodges-Lehmann estimators, and Fisher's test were used.

Results. Doxepin patients (n=78, 96% white, 76% male) were median age 62 years (range=26-87); diphenhydramine-lidocaine-antacid patients (n=76, 88%, 76%) were median age 60 years (23-82); and placebo patients (n=76, 93%, 75%) were median age 60 years (31-94). Pain decreased 12 (doxepin), 12 (diphenhydramine-lidocaine-antacid), and 8.7 (placebo) points. The between-group difference was 2.9 points (95% CI=0.2-6; *P*=.02) for doxepin vs. placebo and 3 (0.1-5.9; *P*=.004) for diphenhydramine-lidocaine-antacid vs. placebo. Versus placebo, more doxepin-induced drowsiness (1.5 points [0-4]; *P*=.03), unpleasant taste (1.5 [0-3]; *P*=.002), and stinging/burning (4 [2.5-5]; *P*<.001) were reported. Maximum-grade 3 adverse events occurred in 4% of doxepin patients, 4% of diphenhydramine-lidocaine-antacid patients, and 2% of placebo patients. Six percent of doxepin patients and no diphenhydramine-lidocaine-antacid patients reported fatigue. Post-hoc exploratory responder analyses: 80% of doxepin (*P*=.14 vs. placebo), 86% of diphenhydramine-lidocaine-antacid (*P*=.02), and 68% of placebo patients responded (≥3.5 points area-under-the-curve reduction).

Commentary. Is this a negative or positive study? The authors used a change of 3.5 points using a statistical approach and as a measure for group changes in mucositis. I do not believe this is the appropriate way to use minimal important clinical differences. Two other approaches to assess clinical differences are by patient global assessment of response (anchor method) or by some external event (such as mucositis severity in this case). There are 2 steps in the use of important changes in trials. The first is to establish important changes; the second is to assess the proportion of patients who achieve important differences.[2] In this trial, the proportion of patients with important changes in the primary outcome was statistically greater in the diphenhydramine-lidocaine-antacid group compared with placebo. The abstract leads one to believe this is a negative trial based on group changes in scores; however, the interpretation of the study really depends on how one uses clinically meaningful differences.

Bottom Line. By responder analysis, diphenhydramine-lidocaine-antacid mouthwash is superior to placebo in the treatment of radiation mucositis.

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

Source. Sio TT, Le-Rademacher JG, Leenstra JL, et al. Effect of doxepin mouthwash or diphenhydramine-lidocaine-antacid mouthwash vs placebo on radiotherapy-related oral mucositis pain: the alliance A221304 randomized clinical trial. *JAMA.* 2019;321(15):1481-1490.

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PC-FACS Feedback

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

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