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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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Rave Reviews

Summaries With Commentaries

Circulating Heparan Sulfate Fragments to Treat Cognitive Dysfunction in Septic Patients

Background. Septic patients frequently experience persistent cognitive impairment (CI).[1,2] Does hippocampal penetration of circulating heparan sulfate (HS) fragments induce septic CI?

Design and Participants. This study used mouse (*ex vivo* and *in vivo*) and human studies to investigate whether hippocampal penetration of circulating HS fragments induces brain-derived neurotrophic factor (BDNF) sequestration, impairing long-term potentiation (LTP) (a BDNF-mediated process responsible for spatial memory formation) and inducing septic CI. Samples were from patients in the Neurocognitive Impairment in Respiratory Failure and Shock study, a substudy of the Molecular Epidemiology of Severe Sepsis in the

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ICU (MESSI) cohort (a prospective cohort of University of Pennsylvania Hospital intensive care unit [ICU] patients); controls were normal blood donors. Analyses included Tukey's criteria and t-tests.

Results. Sepsis- or endotoxemia-surviving mice experienced loss of hippocampal LTP. Memory impairment occurred despite preserved hippocampal BDNF content and was reversed by stimulating BDNF signaling (via BDNF receptor TrkB agonist), suggesting the presence of a local BDNF inhibitor. Sepsis was associated with endothelial glycocalyx degradation, releasing HS fragments (of sufficient size and sulfation to bind BDNF) into circulation (mice and humans). HS fragments penetrated the hippocampal blood—brain barrier during sepsis and inhibited BDNF-mediated LTP (LTP was rescued via TrkB agonist perfusion over mouse hippocampal slices). Glycoarray analyses demonstrated that HS-BDNF avidity increased with sulfation at the iduronic acid 2-O-position and the glucosamine N-position. Circulating HS in endotoxemic mice and septic humans was enriched in 2-O— and N-sulfated disaccharides; the presence of these sulfation patterns in septic patients' plasma at ICU admission predicted CI 14 days post-ICU discharge or at hospital discharge (MoCA score <21 or cognitive inability to perform the test). All $P<.05$.

Commentary. Encephalopathy is common in patients with sepsis and management remains difficult. Septic CI experienced by patients impairs quality of life, limits the patients' ability to return to work, and hinders effective shared decision making, a key component of patient-centered health care. This interesting study in mice, and later conducted in a human clinical trial, explores the concept of how cognitive dysfunction may be the result of not only the inflammatory and/or ischemic injury experienced during critical illness but also from specific mediators such as circulating heparan fragments with specific sulfation patterns, which interfere with BDNF/TrkB signaling. If borne out in future studies, identification of 2-O— and N-sulfated heparin fragments could become part of the evaluation process for predicting patients at risk for CI, and treatments directed at preserving BDNR/TrkB signaling and hippocampal LTP could be developed to prevent CI.

Bottom Line. Circulating HS fragments may help identify septic patients at risk for CI.

Reviewer. Jacob J. Strand, MD FACP FAAHPM, Mayo Clinic Center for Palliative Medicine, Rochester, MN

Source. Hippensteel JA, Anderson BJ, Orfila JE, et al. Circulating heparan sulfate fragments mediate septic cognitive dysfunction. *J Clin Invest.* 2019;129(4):1779-1784.

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Using Clinician-Family Communication About Patients' Values and Preferences to Make Treatment Decisions

Background. Critical care medical technology is advancing rapidly.[1-3] How much do clinicians and surrogates incorporate critically ill patients' values/preferences into decisions?

Design and Participants. This study evaluated how often clinicians and surrogates exchange information about incapacitated intensive care unit (ICU) patients previously expressed values/preferences and deliberate and plan treatment based on these factors during prognosis- and goals of care—related conferences. Secondary analysis of a prospective, cohort study (2009-2012) of audio-recorded clinician-family conferences at 13 ICUs (6 US academic and community medical centers) was conducted using the Wilcoxon rank-sum test. Eligibilities: decision-making incapacity, acute respiratory distress syndrome, and predicted in-hospital mortality ≥50%.

Results. In this study, 249 patients (mean [SD] age, 58 [17] years; 55% male; 75% white), 450 surrogates (49 [14], 34% male, 58% spouses/children), and 141 clinicians (51% attendings and 48% trainees) participated. Two hundred forty-four conferences discussed goals of care; 26% (95% CI, 20%-31%) contained no values/preferences-related information exchange or deliberation. In the 68% (63%-74%) that did, clinicians asked mean 2.3 (median=1; IQR=0-3) values/preferences-related questions). Values discussed included willingness to live in a nursing home (36%) and avoiding prolonged life support (34%). Fifty-six percent (50%-62%) of conferences contained no deliberation about how to apply values/preferences to the clinical decision. Forty-four percent (38%-51%) of conferences included deliberation about applying values/preferences (clinicians made mean 1.6 [median=1; IQR=0-2] statements and surrogates made mean 2.1 [median=1; IQR=1-3] statements). Overall, 7.4% and 5.7% of conferences contained some discussion of how patients would feel about prolonged physical or cognitive/emotional impairment. Clinicians asked surrogates to make substituted judgments about which treatment patients would choose 64 times (40 conferences). In 20 conferences, clinicians recommended treatments based on surrogates' values/preferences-related statements.

Commentary. It is particularly interesting that with all the communication tools at our fingertips, we continue to struggle with incorporating patients' values and preferences into treatment decisions. I find it disconcerting that only 8.2% of conferences in this study included patient values/preferences-based recommendations. This gives me great pause and begs the question: why? Is it a knowledge deficiency that can be remedied through education of surrogates or clinicians? Is it an ethical or moral dilemma among clinicians who are afraid to ask about values because they worry they will lead to treatment recommendations that are contrary to their values? Lastly, how much of this is a healthcare systems issue? Do our current electronic health record and payment/reimbursement models set us up for success or cripple our efforts?

Bottom Line. To get at the heart of the matter and have a significant impact, we must continue to ask why. The answer is likely multifactorial and complex.

Reviewer. Timothy Mark Corbett, MD MA HMDC FAAHPM, Trellis Supportive Care and Wake Forest School of Medicine, Winston-Salem, NC

Source. Scheunemann LP, Ernecoff NC, Buddadhumaruk P, et al. Clinician-family communication about patients' values and preferences in intensive care units [published online ahead of print April 1, 2019]. *JAMA Intern Med.* https://doi.org/10.1001/jamainternmed.2019.0027.

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Effect of End-of-Life Care in Patients Exposed to Home-Based Palliative Care Versus Hospice

Background. Palliative care improves quality of life for patients with serious illness and their caregivers.[1-3] How does home-based palliative care (HomePal) compare against hospice-only (HO) or neither (No-HomePal-HO)?

Design and Participants. This study compared end-of-life care in decedents receiving HomePal vs. either HO or No-HomePal-HO. Retrospective cohorts from an ongoing study (2011-2016) of hospital-to-home care transition within a large integrated California healthcare system were eligible if they had ≥1 hospitalization ≤12 months predeath (discharged alive), a prognosis of ≤12 months, met Medicare guidelines for receipt of home health to include a skilled nursing need, were homebound, and were enrolled for ≥12 months. Physicians, nurses, social workers, therapists, home health aides, and chaplains provided HomePal. Utilization data were extracted from administrative, clinical, and claims databases, and death data were obtained from state and national indices. Days at home equaled days not spent in the hospital or in a skilled nursing facility (SNF). Descriptive statistics, log binomial models, and linear regressions were used.

Results. HomePal patients (n=7,177; mean age, 82±8.61; 51% female; 72% white) were enrolled for median 43 days and had comparable hospice length of stay vs. HO (n=25,102; 82±8.50; 51%; 77%) (median=13 vs. 12 days). HomePal vs. HO (59% vs. 60%) at-home deaths were higher than No-HomePal-HO (n=22,472; 80±8.47; 46%; 70%) (16%). For patients surviving ≥6 months post-HomePal admission, the number of days at home in the last 6 months of life were mean 163±30 vs. 161±30 (HO) vs. 149±40 (No-HomePal-HO) and 25±8, 24±8, and 18±11 for the last 30 days of life. HomePal patients had lower risk of hospitalizations (relative risk [RR]=.58-.87) and SNF stays (RR=.32-.77) vs. HO and No-HomePal-HO (P<.05).

Commentary. Several prior studies have demonstrated longer lengths of stay on hospice for patients receiving HomePal,[4-6] which is how many hospice programs offset the costs of these programs. In contrast, this study shows equivalent hospice median length of stays between the HomePal group and the HO group. So, in effect, this study answers a new question: Does HomePal add additional value to lowering healthcare utilization beyond simply extending traditional hospice? This study evaluates a home health—based palliative care intervention on what looks to be a hospice-eligible population (median survival of 90 days). Even though one-third of the HomePal group never transitioned to hospice, this group still had better utilization outcomes. It is uncertain if these results can be generalized to other populations and program structures.

Bottom Line. HomePal within a home health framework provides additional benefits by reducing healthcare utilization beyond the benefits of extending traditional hospice length of stay.

Reviewer. Laura Patel, MD, Transitions LifeCare, University of North Carolina School of Medicine, Raleigh, NC

Source. Wang SE, Liu IA, Lee JS, et al. End-of-life care in patients exposed to home-based palliative care vs hospice only. *J Am Geriatr Soc.* 2019;67(6):1226-1233.

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Evaluation of the Interrater Reliability of End-of-Life Medical Orders in the Physician Orders for Life-Sustaining Treatment Form

Background. The Physician Orders for Life-Sustaining Treatment (POLST) paradigm was developed to increase the chances of patients' end-of-life values/preferences being respected.[1,2] What is the interrater reliability of medical orders documented in POLST forms?

Design and Participants. This cross-sectional study in a Brazil public university hospital assessed interrater reliability of the POLST form completion process to capture end-of-life treatment preferences. Two independent researchers interviewed the same patients or decision-making surrogates during a single hospitalization episode within a 1-7 day timeframe. Eligible participants were hospitalized adults aged ≥21 years who were expected to remain hospitalized for ≥4 days and whose attending physician responded "no" to: "Would I be surprised if this patient died in the next year?" Interviewers were trained in the advance care planning (ACP) conversation approach based on the Coalition for Compassionate Care of California POLST conversation model. Fisher's test, Wilcoxon rank-sum test, and κ-statistics were used.

Results. Participants (N=64) were 83% patients (mean [SD] age, 64 [14] years; 55% female; 72% white) and 17% surrogates (73% female; 10 were patients' children, and 1 was a wife). The median (IQR) Charlson comorbidity index was 3 (2-4), and the median (IQR) Palliative Performance Scale value was 80% (60%-90%). In 5 cases (8%), disagreement in ≥1 order was found in the POLST form, changing from the first to second interview. Catholics and Evangelicals had less between-interview disagreement vs. Buddhists, Spiritists, or those with no religion ($P<.05$). The κ-statistics were .92 (95% CI, .8-1) for cardiopulmonary resuscitation, .89 (.76-1) for level of medical intervention, and .92 (.83-1) for artificially administered nutrition.

Commentary. There is a great deal of effort being put forth nationally to increase ACP completion and metrics like "presence of an ACP note" or "scanned advance directive." This study of relatively healthy patients from Brazil shows that interrater reliability of orders derived from structured ACP conversations is quite high, but it is not 100%. Remembering that ACP is a process, not an event, and that patients may change their mind as their circumstances change or time passes is crucial. A clinician (or health-system leader) who asserts that ACP has been completed based on a single conversation is unlikely to fully understand the nuanced goals, values, and preferences of a person. Asking a person what they value is better than not doing so, but the answer should be revisited as circumstances change.

Bottom Line. Medical orders that result from structured ACP conversations have high interrater reliability; however, multiple cases of disagreement seen in this study leave open concerns regarding changing preferences or the inherent subjectivity of ACP.

Reviewer. Christopher A. Jones, MD MBA HMDC FAAHPM, University of Pennsylvania Health System, Philadelphia, PA

Source. Lovadini GB, Fukushima FB, Schoueri JFL, et al. Evaluation of the interrater reliability of end-of-life medical orders in the physician orders for life-sustaining treatment form. *JAMA Netw Open.* 2019;2(4):e192036.

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Disparities in End-of-Life Care for Younger Patients with Complex Chronic Conditions

Background. Families of children with complex chronic conditions (CCCs) report unmet medical needs.[1,2] What socioeconomic/clinical disparities exist in medically intense end-of-life (EOL) care rates for children with CCCs?

Design and Participants. This retrospective, population-based analysis determined sociodemographic/clinical factors associated with inpatient EOL intensity indicators using a California State database of children, adolescents, and young adults ages 1-21 years who died 2000-2013. Intensity indicators included: (1) hospital death, (2) receipt of medically intense interventions (MIIs) including intensive care unit (ICU) admissions ≤30 days predeath, and (3) having ≥2 intensity markers (IMs) (including hospital death). Descriptive statistics and multivariable logistic regression were used.

Results. Patients (n=8,654; 47% neuromuscular, 43% malignancy, and 42% cardiovascular) were mean age 12 (SD=6.8) years. Sixty-six percent died in-hospital, 36% had MIIs (11% CPR, 4% hemodialysis, 24% intubation, and 34% ICU), and 35% had ≥2 IMs. Children with cardiovascular, metabolic, neuromuscular, and renal conditions were more likely to have MIIs; children with congenital/genetic, gastrointestinal, malignancy, or respiratory CCCs were less likely. Late adolescence (15-21 years: OR=1.4 [95% CI, 1.2-1.6]; reference=5-9 years), low-income neighborhood (<2X the federal poverty level [FPL]: OR=1.3 [1.1-1.6]; 2-4XFPL: OR=1.2 [1-1.4]; reference=4XFPL), and living >6 miles from a specialty center (6-20 miles: OR=1.2 [1-1.3]; ≥21 miles: OR=1.1 [1-1.3]; reference=<6 miles) were associated with MIIs. Children with cardiovascular, gastrointestinal, hematologic/immunologic, metabolic, neuromuscular, renal, and respiratory CCCs were more likely to have ≥2 IMs; children with congenital/genetic and malignancy CCCs were less likely. Late adolescence (OR=1.3 [1.1-1.5]), minority status (Hispanic: OR=1.3 [1.1-1.4]; other: OR=1.3 [1.1-1.5]; reference=non-Hispanic white), living >6 miles from a specialty center (6-20 miles: OR=1.2 [1-1.3]; ≥21 miles: OR=1.2 [1.1-1.3]; reference=<6 miles), and low-income neighborhood (<2XFPL: OR=1.3 [1.1-1.6]; 2-4XFPL: OR=1.2 [1-1.4]; reference=>4XFPL) were associated with ≥ 2 IMs. All *P*<.05.

Commentary. Two-thirds of the children in this sample died in the hospital. MIIs at the EOL were more frequent in late adolescents, ethnic minorities, low-income families, and patients living far from a specialty center. Children with cardiovascular and neuromuscular CCCs received the most interventions in comparison to those with malignancy and genetic CCCs. For each CCC, hospitalized children had more MIIs than those who died at home. Management disproportionate to prognosis could be because of cultural factors, toxic stress, systems bias, and poor access to hospice/support services, resulting in a delay in having a goals of care discussion. Because pediatric palliative care (PPC) involvement is associated with a lower likelihood of resuscitation at EOL,[3] the gap in PPC coverage may be contributing to higher-intensity EOL care.

Bottom Line. Families' goals may change as the illness evolves.[4] Timing of these discussions and poor access to PPC in hospitals and the community has resulted in a disparity in care at the EOL.

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

Source. Johnston EE, Bogetz J, Saynina O, Chamberlain LJ, Bhatia S, Sanders L. Disparities in inpatient intensity of end-of-life care for complex chronic conditions. *Pediatrics.* 2019;143(5). pii: e20182228.

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Effects of Intervention for Hospice Family Caregivers

Background. Informal family end-of-life caregivers are at risk for depression, deteriorating health, financial difficulties, and premature death.[1,2] Can a problem-solving intervention (PISCES) to support hospice caregivers improve caregiver quality of life (QOL)?

Design and Participants. This 4-year trial in 2 large Pacific Northwest hospice agencies assessed the PISCES intervention's impact on caregiver QOL and anxiety. Caregivers were assigned to a group receiving standard care with added "friendly calls" (attention control [AC]), a group receiving standard care and face-to-face PISCES, or a group receiving standard care and PISCES via videoconferencing. PISCES included a structured curriculum delivered in 3 sessions and motivated caregivers to adopt a positive attitude, define problems by obtaining facts, set goals, and generate and evaluate solutions.

The CQLI-R measured QOL, and the GAD-7 measured anxiety. Other measures included the CRA scale, demographics, an exit interview, and a 40-day follow-up telephone survey. One-way ANOVA, multivariate linear regression, χ^2, t-tests, and Bonferroni adjustment were used.

Results. Caregivers (AC: n=172, mean [SD] age 60 [14] years; videoconferencing: n=171, 61 [12]; face-to-face: n=171, 60 [12]) were 75% female and either adult children (55%) or spouses/partners (27%). There were more diagnoses of cancer and cardiovascular disease among ACs, and dementia was more prevalent among face-to-face participants (P=.005). Eighty-one percent completed the follow up. Versus AC, face-to-face caregivers had reduced anxiety (-1.31 [95% CI, -2.11-.50]; P=.004) and improved social (.57 [.19-.95]; P=.01), financial (.57 [.21-.93]; P=.004), and physical quality of life (.53 [.19-.87]; P=.01) postintervention. There were no differences in the videoconferencing condition vs. AC. Intervention durations were mean 37 days (face-to-face), 38 days, (videoconferencing), and 30 days (AC).

Commentary. There is a lack of scientific evidence on supportive interventions for caregivers in hospice. In this robust, first-of-its-kind clinical trial of hospice caregivers, the PISCES tool proved very effective when delivered in person; this group of caregivers had statistically and clinically significant postintervention reductions in anxiety and improved QOL. The intervention for the video conference group was statistically as effective as the friendly call group, possibly because using friendly calls for these caregivers is itself an intervention. Hospice agencies may consider delivering a combination approach to caregiver intervention: for example, implement a first session in person and follow-up sessions via video conferencing based on staffing, cost, and access.

Bottom Line. Hospice caregivers can benefit from structured cognitive-behavioral interventions such as the PISCES tool, especially if delivered face-to-face.

Reviewer. Kate Aberger, MD FACEP, St. Joseph's Health, Paterson, NJ

Source. Demiris G, Oliver DP, Washington K, Pike K. A problem-solving intervention for hospice family caregivers: a randomized clinical trial [published online ahead of print April 4, 2019]. *J Am Geriatr Soc.* https://doi.org/10.1111/jgs.15894.

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Analgesic Effects of Pharmaceutical-Grade Cannabis in Chronic Pain Patients with Fibromyalgia

Background. Pharmaceutical alternatives to opioid treatment for chronic pain might be found in the chemicals of the cannabis plant.[1,2] What are the analgesic effects of inhaled pharmaceutical-grade cannabis in patients with fibromyalgia?

Design and Participants. This 4-way crossover trial explored the analgesic effects of inhaled pharmaceutical-grade cannabis in adult female chronic pain patients with fibromyalgia. Cannabis varieties tested were: Bedrocan (22 mg Δ^9-tetrahydrocannabinol [THC], <1 mg cannabidiol [CBD]), Bediol (13 mg, 18 mg), Bedrolite (<1 mg, 18 mg), and a placebo variety without THC/CBD. Inclusion criteria were: a pain score ≥5 for most of the day (verbal pain scale: 0=no pain, 10=most pain imaginable) and positive diagnostic criteria of the 2010 American College of Rheumatology. After 1 vapor inhalation, THC/CBD plasma concentrations, pressure and electrical pain thresholds, spontaneous pain scores, and drug high were measured for 3 hours. Analyses included a mixed model, χ^2, and Spearman's ρ.

Results. Participants (N=20) were mean age 39±13 years, weighing mean 82±20 kg (BMI=29±7 kg/m^2). No treatment had an effect greater than placebo on spontaneous or electrical pain responses, although more Bediol-receiving subjects displayed a 30% (but not 50%) decrease in pain scores vs. placebo (90% vs. 55%; n=18; P=.01). Spontaneous pain scores correlated with drug high magnitude for Bedrocan and Bediol (ρ=-.5; P<.001). THC-containing varieties caused an increase in pressure pain threshold vs. placebo (P<.01) (especially Bediol, P<.001). CBD increased THC plasma concentrations but diminished THC-induced analgesia, indicating synergistic pharmacokinetic but antagonistic pharmacodynamic interactions of THC and CBD. Nonserious adverse effects included drug high in 40%-80%, dizziness in 10%-20%, and nausea in 5%-30% of participants (P>.05 between active treatments).

Commentary. There is growing interest among patients in using medical cannabis for the treatment of pain. Yet, the research has been limited and advising patients on what products to use has been challenging. A 2016 Cochrane Review concluded there was no convincing, unbiased, high-quality evidence suggesting the value of cannabinoids in fibromyalgia treatment.[3]

This small, highly controlled study tested 3 types of pharmaceutical-grade inhaled cannabis with varying levels of THC and CBD on acute pain models. None were better than placebo at reducing spontaneous or electrical pain responses, but THC-containing varieties did increase pressure pain thresholds. The results of this study are contrary to long-held views that CBD-containing products might be better tolerated and more beneficial for the attenuation of pain.[4] In this study, many patients complained of drug highs, regardless of treatment. The authors also noted that although CBD increased THC serum concentrations, it also diminished THC-induced analgesia.[5] More research is needed to understand the pharmacokinetic and pharmacodynamic interactions and appropriate dosing strategies of THC and CBD in the management of chronic pain.

Bottom Line. THC, but not CBD, may be more effective in the treatment of fibromyalgia pain.

Reviewer. Jennifer Pruskowski, PharmD BCPS BCGP CPE, University of Pittsburgh School of Pharmacy, UPMC Palliative and Supportive Institute, Pittsburgh, PA

Source. van de Donk T, Niesters M, Kowal MA, Olofsen E, Dahan A, van Velzen M. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. *Pain.* 2019;160(4):860-869.

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Rave Reviews

Currie ER, McPeters SL, Mack JW. Closing the gap on pediatric palliative oncology disparities. *Semin Oncol Nurs.* 2018;34(3):294-302.

Disparities (racial, socioeconomic, and geographic) exist within pediatric palliative oncology and much needs to be done to improve both access to, and the quality of, palliative care for pediatric patients. Several innovative, out of the box ideas for how to improve access and enhance care are provided in this review.

Elk R, Felder T, Cayir E, Samuel C. Social inequalities in palliative care for cancer patients in the United States: a structured review. *Semin Oncol Nurs.* 2018;34(3):303-315.

Disparities including ethnicity, socioeconomic, insurance status, rurality, immigrant status, sexual minority status, and physical and/or intellectual disparities exist in access to and quality of palliative care. All patients deserve the same access to and quality of care, but the reality is that this is not the case. We cannot remain complacent; barriers must be overcome, new policies developed and implemented, research funded, and equitable clinical care provided. Without these steps, many oncology patients will continue to suffer needlessly.

PC-FACS Feedback

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