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PC-FACS (**F**ast **A**rticle **C**ritical **S**ummaries for **C**linicians 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

Use of Propofol to Reduce Microglia Activation and Repair Neurocognitive Disease Damage

Background. Chronic neuroinflammation has been postulated as a central component in neurological disease progression.[1,2] What are propofol's anti-inflammatory, neuroprotective effects?

Design and Participants. This study investigated propofol, a short-acting intravenous anesthetic agent, for its anti-inflammatory effects on microglia. Using a BV2 cell line to model microglia, inflammatory/anti-inflammatory gene expression was measured after proinflammatory bacterial endotoxin lipopolysaccharide (LPS) and propofol treatment. Extracellular vesicle

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(EV) release also was quantified. To assess neurotoxicity, a neuroblastoma-generated neuronal cell line was treated with LPS-activated microglia-conditioned medium. The study also investigated whether propofol's anti-inflammation effects could be reversed by adding immune-activated microglia-isolated EVs. Analysis used ANOVA with Tukey's test.

Results. LPS induced higher classically activated (M1; inflammatory phenotype) microglial gene expression but lower alternative-activated (M2) microglial gene expression. Propofol pretreatment dose dependently decreased M1-specific gene expression and increased M2-specific genes in LPS-activated microglia. LPS-activated microglia-conditioned medium reduced neuronal viability (indicating that activated microglia mediate neurotoxicity through soluble factors), but propofol pretreatment reduced the neurotoxicity. Western blots of isolated EVs revealed EV markers flotillin-2 and tissue trans-glutaminase (tTG), and LPS increased these levels (confirming that immune activation increases EV biogenesis in BV2 microglia). Propofol treatment decreased flotillin-2 and tTG levels in LPS-stimulated microglial EVs. Nanoparticle tracking analysis revealed that LPS up-regulated EV concentration by about 65%, and propofol reversed LPS-induced EV release from BV2 cells. Lastly, EV treatment reversed propofol-mediated anti-inflammatory and neuroprotective effects (propofol-mediated M1 gene down-regulation and M2 gene up-regulation were reversed), suggesting that propofol reduces proinflammatory microglia activation and microglia-mediated neurotoxicity through inhibition of EV release (all $P<0.05$).

Commentary. Chronic neuroinflammation has been proposed as a trigger for the development of neurocognitive diseases such as Parkinson's, Alzheimer's, multiple sclerosis, and epilepsy. Neuroinflammation triggers microglia cells, leading to enhanced phagocytosis and secretion of factors related to brain repair and regeneration; however, prolonged inflammation leads to degeneration and brain cell death.

Propofol is a short-acting, general anesthetic referred to as "milk of amnesia" that is used for patients undergoing surgery. In the intensive care unit setting, propofol often is combined with fentanyl for rapid, easily reversible sedation for intubated patients.

This study highlights the potential of propofol, or a mimetic, to be used for neuroprotection and repair in neurocognitive diseases along with other anti-inflammatory drugs including nonsteroidal anti-inflammatory drugs,[3] glucocorticoids, and disease-modifying antirheumatic drugs such as methotrexate currently being studied.[4]

Bottom Line. Propofol significantly inhibited EV release by microglial cells exposed to LPS and decreased proinflammatory macrophage M1 gene expression while alternatively promoting anti-inflammatory macrophage M2 gene expression.

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

Source. Liu J, Li Y, Xia X, et al. Propofol reduces microglia activation and neurotoxicity through inhibition of extracellular vesicle release. *J Neuroimmunol.* 2019;333:476962.

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Identifying Pressures on General Practitioners in Dealing with Euthanasia or Assisted Suicide

Background. Dutch law states that physicians may go unpunished if they perform euthanasia or physician-assisted suicide (EAS) according to the formulated criteria of due care.[1] What pressures do general practitioners (GPs) experience when dealing with EAS requests?

Design and Participants. This qualitative study explored GPs' pressures when dealing with EAS requests by conducting semistructured in-depth interviews with Dutch GPs (focusing on actual cases). Interview data collection used the principles of constant comparison and the purposive selection of participants. Exclusions were having principle objections against EAS (eg, religious reasons) and having no EAS experience. Interviews were transcribed and analyzed via the framework method.

Results. In this study, 15 GPs (60% male and 53% aged 46−55 years) described a total of 36 EAS request cases in which they experienced pressure. Pressure categories were emotional blackmail (patients threatening suicide or family members threatening to kill the patient), control and direction by others (patient/family feels so convinced they are in control of the euthanasia process that they leave little space for GPs to form their own judgment), doubts about

fulfilling the criteria (feeling forced to decide in a situation that seems "too soon"), counter-pressure by the patient's relatives (GPs are prepared to grant the patient's request but experience pressure from the patients' relatives who oppose), time pressure around referred patients (lacking time to develop a trusting relationship yet feeling no other option than to continue the process a colleague already started), and organizational pressure ("takes more time than we get refunded…takes a lot of energy and thinking" and may interfere with GPs' personal lives).

Commentary. EAS both require a degree of agency by the physician involved. Understanding sources of pressure that may influence this agency is important as public policy around EAS continues to evolve. Understanding EAS's impact on physicians' other work and family life also is important to ensure access and sustainability and to explore whether facilitating patients' expression of authority over their lives when they wish to control the time and manner of their death should be part of the role of medicine.[2] Importantly, no distinction between EAS was made in this paper; the role of the physician varies in each. Only physician-assisted suicide occurs in the Unites States and much of the world.

Bottom Line. This qualitative study identifies several sources of possible influence on the agency of physicians involved in EAS and the effects on those physicians that may need to be addressed at a systems level.

Reviewer. Beth Popp, MD FACP HMDC FAAHPM, Brookdale Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

Source. de Boer ME, Depla MFIA, den Breejen M, Slottje P, Onwuteaka-Philipsen BD, Hertogh CMPM. Pressure in dealing with requests for euthanasia or assisted suicide. Experiences of general practitioners. *J Med Ethics.* 2019;45(7):425-429.

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2. Snyder Sulmasy L, Mueller PS; Ethics, Professionalism and Human Rights Committee of the American College of Physicians. Ethics and the legalization of physician-assisted suicide: an American College of Physicians position paper. *Ann Intern Med.* 2017;167(8):576-578.

Effect of Sexual Orientation on Cancer Survivors' Access to Care and Quality of Life

Background. Healthy People 2020 aims to achieve health equity through improvements in healthcare access.[1,2] Does sexual orientation affect care access?

Design and Participants. This study determined differences in cancer survivors' care access by sexual orientation and examined associations between care access and quality of life. Secondary analysis was conducted on Behavioral Risk Factor Surveillance System[3] data (2014-2017) regarding adult men and women self-reporting a history of cancer. Sexual minorities self-reported as lesbian, gay, bisexual, or other, versus heterosexual. Poor care access meant lacking health insurance, delaying care, avoiding care because of costs, or lacking a trusted physician. Mental/physical quality of life was measured by the number of days with poor mental health and a question regarding poor physical health within 30 days. Cognitive deficits were difficulty concentrating, remembering, or making decisions because of a physical/mental/emotional condition. Cumulative-logit models and logistic regressions were used.

Results. Among 70,524 survivors, 1,931 were sexual minorities. Versus heterosexuals, minorities were mean age 10 years younger and less often married, and minority (vs. heterosexual) men were more educated. Minority (vs. heterosexual) women had more access deficits (43% vs. 28%; $P<.0001$), whereas access was similar in men regardless of sexual orientation. Among minority women, those with access deficits had higher odds of poor physical quality of life vs. heterosexual women (aOR=2 [95% CI=1.2−3.4] vs. 1.3 [1.2−1.5]), poor mental quality of life (1.8 [1.1−3.1] vs. 1.5 [1.3−1.7]), and difficulties concentrating (2 [1.2−3.5] vs. 1.7 [1.4−1.9]). Minority men with access deficits had greater odds of difficulty concentrating vs. heterosexual men (4.3 [2−9.3] vs. 1.5 [1.2−1.9]). Among men, minorities had increased odds of poor mental quality of life (1.49 [1.11−2.01]; all $P<.05$).

Commentary. Although sexual minorities often are studied together, populations under this umbrella term face different challenges and have unique healthcare needs.[4] This study confirms prior documentation that access to care is poorer among sexual minority women[5] and extends this finding by linking this deficit with poorer health outcomes in cancer survivors. Among sexual minority men, while access to care was not poorer, mental health was worse, independent of access. Causal relationships in health disparities are complex and intersectional. Overt discrimination can lead to substandard care, stress, and risky behavior.[6] Insensitive clinician communication is associated with adverse patient health behaviors.[7] Systems barriers, such as lack of ability to

obtain spousal insurance coverage prior to 2015, affect access to care.[8] Lack of research is one of the systems factors that frustrates efforts toward health equity.[8] Sexual minorities were only recently included as a disparity population for National Institute of Health research purposes.[9]

Bottom Line. The underlying causes of the observed patterns in this study are unclear, and better understanding of them is imperative to effectively direct interventions to improve health for sexual-minority cancer survivors.

Reviewer. Elizabeth Chuang, MD MPH FAAHPM, Albert Einstein College of Medicine, Bronx, NY

Source. Boehmer U, Gereige J, Winter M, Ozonoff A. Cancer survivors' access to care and quality of life: do sexual minorities fare worse than heterosexuals? *Cancer.* 2019;125(17):3079-3085.

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The Clinical Course After Long-Term Acute Care Hospital Admission

Background. Long-term acute care hospitals (LTACHs) differ from acute care hospitals and skilled nursing facilities by focusing on treating patients who require extended inpatient care.[1] What are the long-term outcomes after LTACH admission?

Design and Participants. This retrospective, observational, cohort study used 5% Medicare data (2009-2013) to examine long-term clinical course outcomes, including survival, recovery, and healthcare utilization patterns, of hospitalized fee-for-service beneficiaries aged ≥65 years who were transferred to an LTACH. Patients were followed for ≤5 years postadmission. Patients without Medicare Parts A/B, those with Medicare Advantage at any time in the prior 12 months, and those with an LTACH admission ≤12 months before the index care episode were excluded. Kaplan-Meier analyses, log-rank tests, Cox proportional-hazards models, Fine and Gray cumulative incidence functions, and descriptive statistics were used, and a heat map examined healthcare use patterns.

Results. Patients (N=14,072; 40% respiratory diagnosis) were 41% aged ≥80 years, 53% female, and 77% white. Median followup was 0.67 years (IQR=0.12−2.07). Median survival was 8.3 months, and 1- and 5-year survival rates were 45% and 18%, respectively. Survival rates were lower among patients transferred to LTACH vs. not ($P<.001$). Following LTACH admission, 53% of patients never achieved a 60-day recovery. In the first year postadmission, patients spent two-thirds of their remaining life as inpatients (median=66%; IQR=21%−100%). Thirty-seven percent died as inpatients, never returning home postadmission. Sixteen percent enrolled in hospice, with median 10 total hospice days (IQR=3−46). During the preceding hospitalization and index admission, 31% received ≥1 artificial life-prolonging procedure (feeding tube 22%, tracheostomy 19%, and hemodialysis 8.9%), and 1% had a palliative care physician consultation.

Commentary. LTACH patients face a median prognosis worse than most advanced disease states. Although many LTACH patients may derive great benefit from palliative care, little is known about

how to effectively deliver it to this population. First, the reasons for low rates of palliative care referral upstream of LTACH admission are unclear. Hospital and regional factors are more predictive of LTACH admission than patient factors.[2] Similar systematic biases may underlie poor palliative care uptake among LTACH patients—an important consideration for future interventions. Second, LTACH patients may not be able to access palliative care. Care may be fragmented, and many patients remain institutionalized within LTACHs or skilled nursing facilities where palliative care is frequently unavailable. Third, few studies have elucidated what building blocks constitute effective palliative care interventions in this population.[3]

Bottom Line. In light of the high mortality and fragmented care afflicting LTACH patients, evidence-based interventions promoting longitudinal palliative care are needed.

Reviewers. Nauzley Abedini, MD MSc, University of California, San Francisco, San Francisco, CA; Eric Widera, MD, Hospice and Palliative Care Service, San Francisco Veterans Affairs Medical Center, University of California, San Francisco, San Francisco, CA

Source. Makam AN, Tran T, Miller ME, Xuan L, Nguyen OK, Halm EA. The clinical course after long-term acute care hospital admission among older Medicare beneficiaries [published online ahead of print August 26, 2019]. *J Am Geriatr Soc.* https://doi.org/10.1111/jgs.16106.

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Effect of Cognitive Behavior Therapy on Severe Fatigue in Childhood Cancer Survivors

Background. Fatigue is a common, disabling late effect in childhood cancer survivors (CCSs).[1] What is the effectiveness of cognitive behavior therapy (CBT) in CCS with persistent severe fatigue?

Design and Participants. This retrospective study evaluated the effectiveness of CBT for persistent severe fatigue in CCS. From 2008 to 2016, 56 CCSs mostly from 1 long-term survivorship clinic presenting with persistent severe fatigue were referred to a tertiary treatment center for chronic fatigue at the Radboud University Nijmegen Medical Center. Inclusion criteria included being a CCS of any age with severe persistent fatigue, receiving a cancer diagnosis before 18 years of age, having a followup from cancer diagnosis of ≥5 years, and being in persistent complete remission of malignancy. Persistent severe fatigue was defined as ≥35 on the Fatigue Severity Subscale of the Checklist Individual Strength (CIS) and a duration of fatigue of ≥6 months. Consecutively referred CCS with persistent severe fatigue were offered CBT (12−14 sessions over 6-8 months).[2] The primary outcome was fatigue severity (CIS). Secondary outcomes were functional impairment (Sickness Impact Profile-8 [SIP8] and the Short Form-36 [SF36] physical functioning subscale), psychological distress (Symptom Checklist 90), and quality of life (EORTC-QLQ-C30). Descriptive statistics and *t*-tests were used (intention to treat). Analysis was per protocol rather than intention to treat.

Results. The mean age of CCSs completing this study (N=25) was 23 years (range=11−42). Mean age at primary cancer diagnosis was 9.7 years (range=0−17), and mean time since primary cancer diagnosis was 13 years (range=5−34). In this study, 76% completed CBT. Fatigue severity (Δ17; CI=12.7−22.1; $P<0.001$), functional impairment (SIP8=Δ470; CI=312−628; $P<0.001$/SF36=Δ12; CI=17−6.3; $P<0.001$), and psychological distress (Δ26; CI=16−35; $P<0.001$) were decreased at second assessment, and quality of life (Δ14; CI=22−4.3; $P=0.005$) was improved. Eighty-eight percent of CCSs reported clinically significant fatigue improvement.

Commentary. This small, single-center study highlights the lifelong challenges, including severe, performance-limiting fatigue, faced by childhood cancer survivors. Although some demographic information is provided, some nuances may have been lost in translation. Rate of accrual is uncertain and there is limited detail regarding the severity of cancer presentation, episodes of delirium, critical illness, and features of postintensive care syndrome—which may be prolonged—in patients and family members in this high-risk population, all of which could have contributed to severe, otherwise unexplained fatigue long after the conclusion of disease-directed therapy.

Bottom Line. Cognitive behavioral therapy was found to be of benefit to childhood cancer survivors experiencing severe, otherwise unexplained fatigue.

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

Source. Boonstra A, Gielissen M, van Dulmen-den Broeder E, Blijlevens N, Knoop H, Loonen J. Cognitive behavior therapy for persistent severe fatigue in childhood cancer survivors: a pilot study. *J Pediatr Hematol Oncol.* 2019;41(4):313-318.

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Association of Initiation of Maintenance Dialysis with Functional Status and Caregiver Burden

Background. The number of elderly patients on maintenance dialysis is increasing.[1] What is the association between dialysis initiation and functional status and caregiver burden?

Design and Participants. This study assessed the association of maintenance dialysis initiation with functional status and caregiver burden in a community dwelling elderly population and determined variables associated with functional change after initiation. Participants with end-stage kidney disease who were enrolled in the Geriatric Assessment in Older Patients Starting Dialysis study underwent geriatric assessment and frailty screening (FFI[2] and GFI[3]) at dialysis initiation. Functional status (ADL[4] and IADL[5]) and caregiver burden were assessed at baseline and after 6 months. Decline was defined as a loss of ≥1 domain in functional status, stable as no baseline-to-followup difference, and improvement as a gain of ≥1 domain in functional status. Logistic regression assessed the association between the combined outcome functional decline/death and potential risk factors.

Results. Participants (N=187; 50% vascular disease) were mean age 75±7 years and 33% female. At initiation (77% in-center hemodialysis, 23% peritoneal dialysis), 79% were care-dependent in functional status. After 6 months, 40% experienced a decline in functional status (mostly due to IADL independence loss [37% decline vs. 17% improvement]), 34% remained stable, 18% improved, and 8% died. For ADL, most remained stable (66%). The prevalence of high caregiver burden increased 23%-38% (P=0.004). In multivariable analysis, age (OR=1.05; 95% CI=1−1.1 per year older at baseline) and frailty defined by high GFI vs. low score (1.97; 1.05−3.68) were associated with functional decline/death. Geriatric assessment scores were not associated with functional decline/death.

Commentary. This is one of the first studies to prospectively assess functional course after initiating dialysis in a community dwelling elderly population with end-stage kidney disease. Strengths include a comprehensive geriatric assessment including measures of ADLs, IADLs, comorbidities, depression, nutrition, and cognition, and caregiver assessments of patient function and caregiver burden. Findings indicate that functional decline was prevalent in the first 6 months, particularly among frail patients and those age ≥75 years old. Decline was primarily because of loss of IADL activities and was confirmed by caregivers' reports. Initiation of dialysis also was associated with increased caregiver burden. These findings suggest that conversations about initiating dialysis should include potential outcomes of worsening functional status and escalating caregiver burden, especially for older, frail patients.

Bottom Line. For frail patients and those older than 75 years, supportive anticipatory guidance about starting dialysis should acknowledge that it might lead to functional decline rather than improved quality of life.

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

Source. Goto NA, van Loon IN, Boereboom FTJ, et al. Association of initiation of maintenance dialysis with functional status and caregiver burden. *Clin J Am Soc Nephrol.* 2019;14(7):1039-1047.

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Using Duloxetine to Treat Cancer-Related Neuropathic Pain in Patients Nonresponsive or Intolerant to Opioid-Pregabalin Therapy

Background. Cancer-related neuropathic pain (CNP) often is resistant to optimal analgesic treatment.[1-3] What is the efficacy of duloxetine for CNP

nonresponsive or intolerant to opioid-pregabalin combination therapy?

Design and Participants. This double-blinded trial (at 12 Japanese specialized palliative care services) tested whether adding duloxetine to treatment regimens reduces pain intensity in patients with CNP nonresponsive or intolerant to opioid-pregabalin combination therapy. Patients with CNP average pain scores (Brief Pain Inventory [BPI]-Item-5) ≥4 in the previous 24 hours who were nonresponsive or intolerant to opioid-pregabalin were eligible (2015-2017). Patients with chemotherapy-induced peripheral neuropathies were excluded. Patients were administered duloxetine 20 mg/day titrated to 40 mg/day or placebo for 10 days. The primary endpoint was BPI-Item-5 on day 10, and responder analysis measured proportions of patients with 30% and 50% pain decreases. Analyses used chi-squared and *t*-tests (intention to treat).

Results. Patients (N=70) were mean age 63±11 years and 61% male. Duloxetine and placebo groups were comparable in age, sex, performance status, primary tumor sites, and average pain intensity (duloxetine=5.6, placebo=5.7). Complete case analysis revealed mean BPI-Item-5 on day 10 of 4.03 (90% CI=3.33−4.74) for duloxetine vs. 4.88 (4.37−5.38) for placebo (P=0.053). Baseline observation carried forward analysis revealed mean BPI-Item-5 on day 10 of 4.06 (3.37−4.74) for duloxetine vs. 4.91 (4.41−5.41) for placebo (P=0.048). Clinically meaningful improvement (≥30%) was reported among 44% (n=15) in duloxetine vs. 18% (n=6) in placebo (P=0.02); 32% (n=11) vs. 3% (n=1) in duloxetine and placebo, respectively, reported reduction ≥50% (P=0.002). There were no day-10 between-group differences in overall quality of life, physical function, or emotional function.

Commentary. The National Comprehensive Cancer Network recommends gabapentinoids in combination with opioids for the treatment of CNP.[4] But what if this regimen fails? The use of serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine has shown a decrease in neuropathic pain as a result of other etiologies.[5] This study evaluated the benefit of duloxetine in CNP unrelieved by dose-optimized opioid-pregabalin regimens while controlling for changes in concurrent analgesics. The addition of duloxetine 20−40 mg/day was found to improve pain in refractory CNP, but there was no difference in overall quality of life, physical function, or emotional function. Prior research has shown that duloxetine improves neuropathic pain, function, and quality of life after 5 weeks of treatment.[6] Although the starting dose for the treatment of chemotherapy-induced peripheral neuropathy is 30 mg/day, the recommend starting dose in diabetic neuropathy is higher (60 mg/day). Perhaps a longer course of treatment and/or higher dosages may demonstrate a more dramatic benefit of duloxetine in CNP. Further research is needed to determine if this benefit is observed with other SNRIs and to define the optimal treatment algorithm for refractory CNP.

Bottom Line. Duloxetine reduces cancer-related neuropathic pain in patients nonresponsive or intolerant to opioid-pregabalin therapy.

Reviewers. Kristin L. Hines, MD, Vanderbilt University Medical Center, Nashville, TN; Sara F. Martin, MD, Vanderbilt University Medical Center, Nashville TN

Source. Matsuoka H, Iwase S, Miyaji T, et al. Additive duloxetine for cancer-related neuropathic pain nonresponsive or intolerant to opioid-pregabalin therapy: a randomized controlled trial (JORTC-PAL08) [published online ahead of print June 26, 2019]. *J Pain Symptom Manage.* pii: S0885-3924(19)30364-1. https://doi.org/10.1016/j.jpainsymman.2019.06.020.

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Rave Reviews

Hanning J, Walker KJ, Horrigan D, Levinson M, Mills A. Review article: Goals-of-care discussions for adult patients nearing end of life in emergency

departments: a systematic review. *Emerg Med Australas.* 2019;31(4):525-532.
This systematic review, written for emergency medicine providers, examined the literature to understand the best way to initiate goals of care conversations in the emergency department (ED) setting. It should come as no surprise that the literature varied significantly; however, it was clear that having more ED goals of care conversations increased hospice referrals and reduced inpatient admissions.

Wool C, Catlin A. Perinatal bereavement and palliative care offered throughout the healthcare system. *Ann Palliat Med.* 2019;8(Suppl 1):S22-S29.
This review provides an outline of perinatal bereavement services available today and focuses on ways to improve this important component of family-centered care. Needed resources and educational opportunities are discussed and the many of the different sites of care (including inpatient, outpatient, and the operating room) and teams involved (including ethics, chaplaincy, and palliative care) are described. Recommendations are made for health systems looking to create a high-quality perinatal bereavement program.

Gabbard J, Jordan A, Mitchell J, Corbett M, White P, Childers J. Dying on hospice in the midst of an opioid crisis: what should we do now? *Am J Hosp Palliat Care.* 2019;36(4):273-281.
This review of the literature aims at the practical, trying to help clinicians navigate serious illness care during the opioid epidemic. This review focuses on hospice care and offers specific recommendations for managing a hospice population, with an emphasis on patients with substance use disorders (SUD) or at risk of developing a SUD.

PC-FACS Feedback

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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.*

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