PC-FACS

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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 pc-facs@aahpm.org.*

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Summaries With Commentaries

Effect of Oxytocin on Nociceptive Hypersensitivity in Pain in Rat Models

Background. Oxytocin has antinociceptive properties.[1] How does the oxytocin system influence nociceptive hypersensitivity?

Model of Neonatal Maternal Separation

Design and Participants. This study tested whether the endogenous analgesic effect of oxytocin (through an action on the nociceptive system) is altered by early life stress, possibly contributing to long-term consequences on pain response. A rat model of neonatal maternal separation (NMS) was used, which induces long-term consequences on brain functions including chronic stress, anxiety, altered social behavior, and visceral hypersensitivity.

Results. Adult NMS rats were hypersensitive to noxious mechanical/thermal stimuli and inflammatory pain. Oxytocin receptor-mediated stress-induced analgesia and oxytocin antihyperalgesia after carrageenan inflammation were unobserved. These alterations were partially rescued via intraperitoneal daily injection during NMS with oxytocin or its downstream second messenger allopregnanolone. Epigenetic involvement in these alterations was confirmed because neonatal treatment with a histone deacetylase inhibitor normalized nociceptive sensitivities and restored oxytocin receptor-mediated stress-induced analgesia and endogenous antihyperalgesia (all $P<.001$).

Recovery from Surgery with Nerve Injury

Design and Participants. This study tested whether pain recovery in rats postsurgery could be reversed by antagonism of spinal oxytocin or vasopressin receptors. Male and female rats underwent partial spinal nerve ligation (PSNL). Effects of nonselective and selective oxytocin and vasopressin 1A receptor antagonists on mechanical hypersensitivity during recovery were assessed. Oxytocin immunoreactivity in the spinal cord (SC) dorsal horn and oxytocin-binding receptor mRNA expression in dorsal root ganglia and SC were measured.

Results. Post-PSNL in both sexes: oxytocin or vasopressin 1A receptor blockade increased mechanical hypersensitivity ($P<.0025$); SC oxytocin levels ($P<.05$) and oxytocin and vasopressin 1A receptor expression increased ($P<.05$).

Commentary. Oxytocin, a peptide hormone, traditionally has been known to play a role in social bonding, sexual reproduction, and childbirth. The oxytocin system is intertwined with the hypothalamic-pituitary stress axis; autonomic nervous system; neurotransmitters such as dopamine, serotonin, and GABA/glutamate; and the immune system. Recently, researchers have identified an oxytocin analgesic system that limits inflammatory sensitization[2] and neuropathic pain[3] and is altered by early life stress[4].

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In NMS rodents, a well-established model of early life stress, a histone deacetylase inhibitor (SAHA) prevented visceral[5], mechanical, and thermal hypersensitivity. In the future, patients with stress-induced alterations in pain circuits may be "rescued" by restoring the oxytocin analgesic system or by reversing the long-term epigenetic changes triggered by early life stress or trauma.

Research on oxytocin highlights the impact of early life stress on a patient's ability to process painful stimuli, which could potentially contribute to pain-related comorbidities such as anxiety and depression. In addition, individual variation of the endogenous oxytocin system based on genetic disposition and environmental influences has been implicated in vulnerability to addiction[6], which is a growing epidemic in our country. The palliative care principle of treating pain and suffering of the patient and addressing the needs of the family, especially children, may have longitudinal impact on processing pain and coping with stress.

Bottom Line. Oxytocin provides antinociception, centrally mediated at the level of the spinal cord and peripherally at the dorsal root ganglion[7], resulting in decreased sensitivity to noxious mechanical/thermal stimuli and quicker recovery from surgical nerve injury.

Reviewer. Rony Dev, DO, Department of Symptom Control and Palliative Medicine, University of Texas MD Anderson Cancer Center, Houston, TX

Sources. Melchior M, Juif PE, Gazzo G, et al. Pharmacological rescue of nociceptive hypersensitivity and oxytocin analgesia impairment in a rat model of neonatal maternal separation. *Pain.* 2018;159(12): 2630-2640.

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Physicians Approach to Care for Dying Patients with Amyotrophic Lateral Sclerosis While Considering the Law

Background. Death with dignity (DWD) legislation excludes patients with amyotrophic lateral sclerosis (ALS) because the drug must be self-ingested and the alternative (euthanasia) is illegal.[1,2] What constitutes an ethical framework for physicians faced with difficult end-of-life situations?

Design and Participants. This essay defines relevant terms raised by the case of a dying patient in Washington who cannot self-administer a lethal prescription. Donald's ALS has progressed; he uses a wheelchair and cannot use his hands for even simple tasks. His declining respiratory function remains intact, but his swallowing is deteriorating. Donald tells his palliative care (PC) physician, Dr. S, he wishes to end his life. In physician aid-in-dying (PAD), physicians prescribe lethal drugs that their patients self-administer, whereas in euthanasia (illegal in the United States), physicians themselves administer lethal drugs. Because of Donald's inability to self-administer, Donald cannot take advantage of Washington's DWD law.

Results. When patients request PAD in states that allow PAD, the authors suggest these steps for physicians: (1) explore the patient's motivations (identify/treat/refer for any psychiatric conditions); (2) obtain the patient's informed consent (explain the alternatives [PC], and consider the patient's decision-making capacity); (3) after learning what brings meaning to the patient's life, discuss prognosis and define goals of care; (4) discuss alternatives (eg, PC, stopping eating/drinking, life-sustaining treatment withdrawal), and ensure the patient is not seeking PAD for lack of financial resources. As a way around physical limitations, if the patient still wants PAD, the family could prepare

the drug and place it in the patient's mouth; the patient would subsequently move his or her head or push the syringe into his or her mouth.

Commentary. Patients with progressive neurological illnesses may be referred to PC teams for symptom management, clarifying goals of care, and advance care planning. In areas where aid-in-dying (AID) is legal, it may be part of the broad discussion with the PC team. PC may be provided during the waiting periods required in most jurisdictions that currently have legal AID. This case study provides a framework for considering how to respond when encountering these situations. Some of the suggestions in this article are ethically and legally controversial and should be considered very carefully and with appropriate guidance. PC clinicians will need to develop an approach to the care of patients who wish for AID but do not qualify under the law.

Bottom Line. Even in areas where AID is legal, some terminally ill patients, especially those with progressive neurological conditions, who might want to utilize AID will be unable to do so legally.

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

Source. Craig A, Dzeng E. How should physicians care for dying patients with amyotrophic lateral sclerosis? *AMA J Ethics*. 2018;20(8):E690-E698.

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2. Emanuel EJ, Daniels ER, Fairclough DL, Clarridge BR. The practice of euthanasia and physician-assisted suicide in the United States: adherence to proposed safeguards and effects on physicians. *JAMA*. 1998;280(6):507-513.

Pharmacist Educational Intervention When Prescribing Inappropriate Medications

Background. About 29% of Medicare beneficiaries aged ≥65 years filled a prescription in 2015 for medication included in the American Geriatrics Society Beers Criteria list of drugs to avoid.[1] Can an educational intervention reduce inappropriate prescribing?

Design and Participants. This cluster randomized trial assessed the effectiveness of a consumer-targeted, pharmacist-led educational intervention on the discontinuation of inappropriate medication among community-dwelling older adults. Community pharmacists in Quebec, Canada were recruited (2014-2017). Patients aged ≥65 years, who were prescribed 1 of 4 Beers Criteria medications (sedative-hypnotics, glyburide, or nonsteroidal antiinflammatory drugs), were recruited from 69 community pharmacies. Intervention-group pharmacists were encouraged to send patients an educational deprescribing brochure parallel to sending their physicians an evidence-based pharmaceutical opinion to recommend deprescribing. Control-group pharmacists provided usual care. Patients, physicians, pharmacists, and evaluators were blinded to outcome assessment. Analysis (intention-to-treat) included generalized estimating equations.

Results. Among 489 patients (mean [range] age 75 [66−96] years; 66% women, 23% aged ≥80 years, and 27% meeting criteria for frailty), 89% completed the trial (n=219 intervention [34 pharmacies] vs. n=218 control [35 pharmacies]). At 6 months, 43% of intervention patients no longer filled prescriptions for inappropriate medication, vs. 12% of control (risk difference [RD]=31% [95% CI, 23%−38%]). Discontinuation of inappropriate medication occurred among 43% (vs. 9.0%) of sedative-hypnotic drug users (RD=34% [25%−43%]), 31% (vs. 14%) of glyburide users (RD=17% [2%−31%]), and 58% (vs. 22%) of nonsteroidal antiinflammatory drug users (RD=35% [10%−55%]; *P* for interaction=.09). No hospitalization-requiring adverse events were reported, however, 38% of patients who attempted to taper sedative-hypnotics reported withdrawal symptoms.

Commentary. Older adults are at risk of polypharmacy. This is especially true in the last stages of life when new medications are prescribed to manage symptoms while chronic preventive medications often are also continued.[2,3] This study demonstrates that a pharmacist-initiated effort to educate patients and their physicians about medication risks can lead to a decrease in prescriptions. It adds to the body of literature that indicates that directly involving patients in decision-making processes to deprescribe can improve deprescription rates. To expand upon this research for a palliative care population, it may be worth exploring the role of pharmacists in providing education not just on potentially harmful medications but also on re-evaluating medications that are unlikely to benefit patients, such as statins for primary prevention in the last year of life or cholinesterase inhibitors in advanced dementia.

Bottom Line. Pharmacist-led educational intervention has the ability to reduce prescription of potentially harmful medications.

Reviewers. Evie Kalmar, MD MS, and Eric Widera, MD; University of California, San Francisco, CA

Source. Martin P, Tamblyn R, Benedetti A, Ahmed S, Tannenbaum C. Effect of a pharmacist-led educational intervention on inappropriate medication prescriptions in older adults: the D-

PRESCRIBE randomized clinical trial. *JAMA*. 2018;320(18):1889-1898.

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2. McNeil MJ, Kamal AH, Kutner JS, Ritchie CS, Abernethy AP. The burden of polypharmacy in patients near the end of life. *J Pain Symptom Manage*. 2016;51(2):178-183.
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Trends in Hospice Discharge and Relative Outcomes Among Medicare Patients with Heart Failure

Background. Median survival among Medicare beneficiaries hospitalized with heart failure (HF) is only 2.1 years.[1,2] What is the state of hospice care for older patients hospitalized with HF?

Design and Participants. This observational cohort study assessed rates of discharge to hospice, posthospice rehospitalization, and in-hospice survival in patients following hospital discharge. Patients (aged ≥65 years) in the Get With The Guidelines—Heart Failure[3] registry linked to Medicare claims data, who were discharged alive from the hospital (2005-2014), were analyzed. Patients with HF discharged to hospice (group A) were compared against patients with advanced HF (based on predefined clinical criteria) who were not discharged to hospice (group B) and other patients with HF in the registry (group C). Pearson χ^2, Kruskal-Wallis, and log-rank tests were used as well as Cox and Fine-Gray models.

Results. In this study, 121,990 patients (438 sites) were included. Three point eight percent were A (median age 86 [IQR=80—90] years; 56% female), 3.6% were B (78 [72—84]; 34%), and 93% were C (81 [74—87]; 55%; all $P<.001$). Group A were more symptomatic, more likely white, and had received higher education than B or C ($P<.001$). Hospice discharges increased 2%—4.9% (2005-2014). The median survival time in A was 11 (IQR=3—63) days, vs. B=318 (78—1105) and C=754 (221—1868; all $P<.001$). Thirty-four percent (vs. 12%) of patients discharged to hospice facilities (vs. home hospice) died in <72 hours ($P<.001$); 15% discharged from hospice lived ≥6 months. Among hospitals with >25 hospice discharges, the median discharge rate was 3.5% (IQR=2%—5.7%). Readmission at 30 days was 4.1% in A, vs. B=27% and C=22% ($P<.001$). Non-white race and younger age were the strongest readmission-from-hospice predictors.

Commentary. This large study contains good and bad news. Hospice use for patients discharged from the hospital with advanced HF increased from 2% to almost 5% over a decade, but median survival remains short: 11 days for all discharged to hospice and only 5 days for those discharged to a facility. The comparator cohort with advanced HF survived for almost a year. This short survival, whether due to very late referrals of those "already-dying" to hospice or hospices' difficulties managing heart failure symptoms in such a way that allows additional longevity, may serve to reinforce to HF clinicians that hospice is for acutely dying patients for whom there is nothing more to do.

Bottom Line. For patients with advanced HF, hospice use is increasing; however, patients discharged with hospice support die much faster than comparator patients who do not receive hospice care.

Reviewer. Christopher A. Jones, MD MBA HMDC FAAHPM, Perelman School of Medicine and the Palliative and Advanced Illness Research Center at the University of Pennsylvania, Philadelphia, PA

Source. Warraich HJ, Xu H, DeVore AD, et al. Trends in hospice discharge and relative outcomes among Medicare patients in the Get With The Guidelines—Heart Failure registry. *JAMA Cardiol*. 2018;3(10):917-926.

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Ethics of Influencing Decisions in Physician-Patient Communications

Background. "Nudges" (physician communication techniques that influence patients' choices) may assist patients in making decisions.[1] Are nudges ethical/appropriate in medical decision making?

Design and Participants. This study assessed whether stakeholders (physicians and laypersons without clinical training) consider nudges ethical/appropriate in medical decision making. Resident physicians and Mechanical Turk workers (nonclinicians) completed an electronic survey consisting of two decision-making vignettes (V1=hospice-endorsing; V2=chemotherapy-

endorsing) describing patients deciding between chemotherapy and hospice care for incurable cancer. Two attributes of each vignette varied randomly among participants: (1) whether or not the patient's decision was influenced by a mistaken judgment (bias) and (2) whether or not the physician nudged the patient (eg, information framing and social comparisons). Participants reported the extent to which the communication was ethical/appropriate and desirable. MANOVA analyses were performed.

Results. Nonclinicians (n=336) were mean (SD) age 32 (10) years, 64% female, and 78% white. Physicians (n=89) were mean age 30 (2) years, 38% female, and 62% white. Physicians and nonclinicians perceived using nudges more positively than not using them, regardless of an initial patient bias (nudge effect: V1: F[8, 78]=16.09, V2: F[8, 78]=7.42; V1: F[8, 325]=16.10, V2: F[8, 325]=33.81, respectively [all $P<.001$]). In V1, nonclinicians evaluated patients' autonomy the same, regardless of nudge presence/absence, and physicians evaluated communications as more acceptable/trustworthy if bias was absent (bias effect: F[8, 78]=2.15, $P=.04$). Contrary to nonclinicians, physicians viewed the V1 (vs. V2) nudge more favorably. Physicians evaluated V1 nudges more positively than nonclinicians (V1: F[8, 203]= 2.16,$P=.032$). Nonclinicians evaluated V2 nudges more positively than physicians (V2: F[8, 201]=3.25, $P=.002$).

Commentary. This study is the first to examine ethical concerns about nudges in preference-sensitive, end-of-life decisions. The findings suggest that both clinicians and nonclinicians view nudges as ethical and appropriate, even if there was no evidence that the patient had a bias in initial judgement. The fact that clinicians evaluated the nudge endorsing hospice care more favorably, while nonclinicians evaluated the nudge endorsing chemotherapy more favorably, suggests that individuals support nudges more when they are consistent with their views. Findings should be interpreted in light of the study design, which used hypothetical vignettes. Future research should collect data among people actually dealing with these decisions.

Bottom Line. This study provides preliminary evidence that both clinicians and nonclinicians view nudges as ethical in the context of treatment decisions at the end of life.

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

Source. Fridman I, Hart JL, Yadav KN, Higgins ET. Perspectives on using decision-making nudges in physician-patient communications. *PLoS One.* 2018; 13(9):e0202874.

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Use of Probiotics for the Prevention or Treatment of Chemotherapy or Radiotherapy-Related Diarrhea

Background. The incidence of diarrhea during chemotherapy/radiotherapy is 50%−80%.[1] Can probiotics prevent/reduce chemotherapy/radiotherapy−induced diarrhea?

Design and Participants. This meta-analysis evaluated the effectiveness of probiotics for prevention/ treatment of diarrhea related to radiotherapy (with/ without chemotherapy) or chemotherapy alone in adults with cancer. The Cochrane Central Register of Controlled Trials (2017), MEDLINE (1946-2017), and Embase (1980-2017) were searched. Two authors independently selected randomized controlled trials, extracted data, and assessed bias. Random-effects models were used.

Results. For prevention of radiotherapy (with/without chemotherapy)-induced diarrhea, authors identified five placebo-controlled studies (n=926): for any diarrhea, risk ratios (RRs) ranged from 0.35 (95% CI=0.26−0.47) to 1 (0.94−1.06; three studies; low-certainty evidence); a beneficial effect of probiotics on quality-of-life could not be demonstrated/refuted (two; low certainty). For probiotic users, time-to-rescue medication was 36 hours longer in 1 study (34.7−37.3), but 1 reported no difference (moderate certainty). Three placebo-controlled studies addressed chemotherapy-induced diarrhea prevention (not quality of life/time to rescue): for any diarrhea, pooled RR=0.59 (0.36−0.96; two; n=106; low certainty); for all other outcomes, a beneficial effect of probiotics could not be demonstrated/refuted (one-two; n=46−106; low certainty). Three studies compared probiotics with another intervention for radiotherapy (with/without chemotherapy)-induced diarrhea (not quality of life/ time to rescue): one (n=21) reported less diarrhea when providing dietary counseling (RR=0.30, 0.11−0.81; very low certainty); in another (n=148), diarrhea occurred less often with probiotics vs. guar gum (odds ratio [OR]=0.38, 0.16-0.89; low certainty); and two (n=63) found less need for rescue in probiotics (RR=0.44, 0.22−0.86; very low certainty). One placebo-controlled study (n=205) addressed radiotherapy-induced diarrhea treatment and could not demonstrate/refute a beneficial effect on average diarrhea grade, time to rescue (13 hours

longer for probiotics, -0.9−26.9 hours), or need for rescue (RR=0.74, 0.53−1.03; moderate certainty).

Commentary. Diarrhea is a very common and troublesome side effect of radiation and/or chemotherapy that adversely affects cancer patients' quality of life and may be difficult to control. Probiotics are live microorganisms thought to work by stimulating the proliferation of bowel epithelial cells and thus aiding in repair of damaged mucosa. The question whether probiotics are helpful in prevention or treatment of radiotherapy- or chemotherapy-induced diarrhea remains largely unanswered, as only low- or very low-certainty evidence currently exists.[2-5] All studies were found to be underpowered and heterogeneous in populations and strain(s) of probiotics used. However, probiotics appear to be safe and some studies found them to be beneficial. Future well-designed studies are necessary.

Bottom Line. Probiotics should not yet be routinely considered for the prevention or treatment of chemotherapy- or radiotherapy-related diarrhea in people with cancer.

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

Source. Wei D, Heus P, van de Wetering FT, van Tienhoven G, Verleye L, Scholten RJ. Probiotics for the prevention or treatment of chemotherapy or radiotherapy-related diarrhoea in people with cancer. *Cochrane Database Syst Rev.* 2018;8:CD008831.

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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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