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**A Novel Finding of Nalbuphine-6-Glucuronide Possessing Potent Antinociceptive Effects**

Background. Nalbuphine, a semisynthetic opioid, is equipotent to morphine in relieving moderate to severe pain and has no serious side effects.1 What are the antinociceptive effects of fully synthesized nalbuphine metabolites?

Design and Participants. This pharmacodynamic study synthesized nalbuphine metabolites, nalbuphine-3-glucuronide (N3G), and nalbuphine-6-glucuronide (N6G) and assessed their analgesic effects in rats. Paw pressure (Randall-Selitto) and cold-ethanol tail-flick (CET) tests were conducted to evaluate analgesic response after nalbuphine, N3G, or N6G intracisternal and intraperitoneal administrations. Antinociception was evaluated by...
calculating area under the time course curve (AUC; trapezoidal method) and duration spent at >50% maximum possible analgesia (%MPA=\[(Test-Baseline)/(Cutoff-Baseline)\]x100%). Animals (n=6/group) were tested at 15, 30, and 45 minutes premedication to obtain an average baseline of aversive time latency and CET latency (each animal its own control). Tail-flick latency was measured over 2.5 hours (15-minute intervals) postadministration. Analysis used one-factor ANOVA with Tukey’s test.

Results. In intracisternal administration, N6G exerted potent antinociceptive effects, with 2.8- and 3.5-times higher AUC values than nalbuphine in the Randall-Selitto and CET tests, respectively. However, N3G showed scarce biological activity in the pain tests. The pain relief durations expressed as elapsed times corresponding to the percent analgesic effect >50% MPA were longer with N6G than with nalbuphine or N3G in both pain tests. In intraperitoneal administration, nalbuphine exerted antinociceptive effects, but N3G and N6G produced no antinociceptive responses. In addition, the pain-relieving durations of nalbuphine in terms of time elapses >50% MPA were <10 minutes in both tests. The highly water-soluble property of N6G likely restricts its antinociceptive effects via common-route administration. All \(P<0.05\).

Commentary. In the current epidemic of death due to opioids, developing effective analgesics with lower abuse potential and decreased toxicity is critical. Nalbuphine, primarily a kappa-agonist/mu-antagonist, effectively antagonizes respiratory depression potential while maintaining an analgesic response and has been reported to have lower risk of abuse.\(^2\) Liang et al. recognized that nalbuphine undergoes glucuronidation in a manner similar to morphine\(^3\) and have shown that, like morphine, the N6G metabolite has improved pain control, whereas the N3G metabolite has minimal analgesia but significant toxicity. Although the animal data in this paper are strong, chemical modifications that permit oral or IV administration of N6G and human clinical trials demonstrating retention of the analgesic and safety profiles are still required.

Bottom Line. Creating safer analgesic medications is critical. This study highlights the potential of drug metabolites, such as N6G, which may provide analgesia without risk for abuse and respiratory depression.

Reviewer. Kenneth Cornetta, MD, Indiana University School of Medicine, Indianapolis, IN


References


Are Patients’ Wishes for DNR and POLST Orders Represented in Their Medical Records?

Background. The Patient Self-Determination Act encourages the documentation of patients’ wishes for resuscitation and life support preincapacitance.\(^1\) Are do-not-resuscitate (DNR) and physician orders for life-sustaining treatment (POLST) orders concordant with patients’ wishes?

Design and Participants. This prospective, single-center study determined whether DNRs created upon hospital admission or POLSTs are consistent with patient preferences and patient (or appointed healthcare agent) awareness of and agreement with these orders. Patients with DNRs and/or POLSTs (2017-2018) were interviewed (\(\leq 48\) hours postadmission) about their awareness of their prognosis, the DNR, and treatment selection within the POLST or living will (LW). Discrepancy rates, changes from DNR to full code, and care preferences were analyzed. Fisher’s exact test, t-test, Mann-Whitney U test, and \(\chi^2\) were used.

Results. Patients (\(N=101\)) were mean±SD age 76±11 years, 55% female, and 85% white. All had DNRs (85% physician created). All patients were DNR; a LW was present in 22% of cases and a POLST in 8%. The median frailty score (4; IQR=2.5) suggested patients required minimal assistance. In interviews, 30% “wanted” cardiopulmonary resuscitation and 63% wanted a trial of medical support (even if aggressive) to see whether improvement occurred. Twenty-five percent (±8.4%) were unaware of the DNR, 50±9.8% were unsure of prognosis, and 40±9.6% felt their condition was not terminal. Overall, 44±9.7% of DNRs were discordant with interview wishes; 38±9.5% were rescinded (further clarifications were required of the 6% not rescinded). Discrepancy was associated with younger, slightly less frail (clinical scoring algorithm) and DNR-unaware patients (\(P<0.001\)).

Commentary. This article is a scientific demonstration of George Bernard Shaw’s reputed quote, “The
greatest problem with communication is the illusion it has occurred.” As we focus on medical errors, this study shows that the likelihood of getting an accurate DNR is close to that of a coin toss! Again, we in the hospice and palliative medicine community are reminded of the importance of effective and ongoing communication with patients and colleagues. Likewise, these astounding numbers sound the alarm for detailed documentation of each patient-centered advance care planning (ACP) discussion focused on shared decision making before and at the end of life using an understandable format.

Bottom Line. Life and death resuscitation orders often are created under time pressures and in circumstances that minimize effective communication and understanding. This can be ameliorated with properly documented ACP discussions prior to life-changing events. Frequent review and discussion are vital (literally) to the patient’s care. It is never “one and done.”

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Reference


Methods for Overcoming Barriers in Palliative Care for Ethnic and Racial Minorities

Background. In 2015, only 25% of hospice patients were non-white, and only 7.1% of the Caucasian patients identified as Hispanic/Latino. How can barriers faced by ethnic/racial minorities when accessing palliative care and end-of-life services be overcome?

Design and Participants. This study reviewed interventional studies that investigated methods for overcoming barriers faced by ethnic/racial minorities when accessing end-of-life services. Inclusion criteria: the study population included ethnic/racial/served minorities in health care, the article focused on healthcare disparities surrounding end-of-life outcomes (advance directives, goals of care, do not resuscitate discussions, or hospice enrollment), and the study investigated an intervention targeted at overcoming a barrier faced by ethnic/racial minorities. The Downs and Black (DB) checklist appraised the studies (≥20=very good; 15–19=good; 11–14=fair; ≤10=poor).

Results. Nine articles (2005-2015) were included, and participants were ~66% female. Minority groups were African Americans (n=4), Hispanics/Latinos (n=3), and Asians or Pacific Islanders (n=2). Settings included outpatient ambulatory clinics, assisted living facilities, home visits, and telephone follow-ups. All involved completed ≥1 face-to-face interview and a survey/questionnaire measuring outcomes including attitudes regarding discussion of end-of-life decisions with providers, preferences for aggressive medical care versus comfort-focused care, advance directive completion, and hospice enrollment. Three main intervention avenues included methods to enhance patient education, increase healthcare access, or improve communication to establish better rapport with the target population. Studies suggested that the traditional, nontargeted delivery of healthcare services and information is insufficient in improving ethnic/racial minorities’ usage of palliative care, and outcomes can be improved through tailored interventions to overcome barriers. The DB score was median=16 (range=13–21). Zero studies had the power to detect between-group significance (one was “high quality”).

Commentary. Significant ethnic/racial disparities exist across health care, even in palliative and end-of-life care. Although there is a fair amount of research documenting healthcare disparities among minority groups, there is a scarcity of research studying potential interventions. This review highlights the paucity and quality of such research. In addition, there were methodological challenges in all 9 studies reviewed: none had the power to detect statistical differences between groups and many ethnic groups were unrepresented. The authors highlight 3 main areas of intervention that are effective in overcoming disparities: patient education, healthcare access, and communication. In addition, they recommended research that focuses on religion/spirituality, interventions to better engage medical interpreters, and innovation that would improve study design, increase recruitment, and decrease dropout rates.

Bottom Line. More quality research is needed to develop tailored interventions to overcome ethnic/racial healthcare disparities in palliative and end-of-life care.

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

References


Adverse Events in Long-Term Care Residents
Transiting From Hospital Back to Nursing Home

Background. Long-term care (LTC) facility residents are especially at risk for adverse events (AEs) after hospital discharge.1,2 What is the prevalence of AEs in LTC residents transitioning from hospital back to LTC?

Design and Participants. This prospective cohort study reported the incidence, type, severity, and preventability of AEs (harm/injury resulting from medical care or failure to provide needed care) in LTC residents transitioning from hospital back to the same LTC facility. Residents were selected from a random sample of New England nursing homes. The main outcome was AEs ≤45 days post-transition. Trained nurse abstractors reviewed nursing home records for the period, and 2 physicians independently reviewed each potential AE to determine whether harm occurred and to characterize the event. Analyses included χ²² tests.

Results. Residents (n=555; 32 nursing homes) were 66% female, 94% white, and mean (SD) age 82 (12) years, and they took part in 762 transitions from hospitals to LTC facilities. Sixty-three percent of discharges were associated with no event and 28% with 1 event. Overall, 379 AEs occurred (incidence rate [IR]=14 [95% CI, 12–15] per 1000 resident days), and 52% were resident care–related: most commonly, pressure ulcers, skin tears, and falls with injury. Healthcare-acquired infections (29%) and drug-related AEs (17%) were the next most common. Of AEs, 52% were characterized as less serious; however, 38% were deemed serious, 7.4% life-threatening, and 2.1% fatal. Seventy-one percent were deemed preventable/ameliorable (IR=9.5 [8.4–11]), with less serious events (vs. more serious [67%]) more often considered preventable/ ameliorable (74%). In addition, resident care–related AEs were more commonly deemed preventable (88%) vs. drug-related AEs (61%) or healthcare-acquired infections (45%).

Commentary. AEs are common in LTC residents following hospitalization. In this study, more than half of AEs occurred within the first 7 days of returning to the facility. A large percentage of these AEs were resident care–related, suggesting inadequate monitoring and resources. Nearly a quarter of AEs occurred on the day of hospital discharge or the day after, suggesting that residents may have been prematurely discharged. With chronic staffing shortages, the ability to increase LTC staffing and support in the week postdischarge likely is challenging. However, that 72% of life-threatening and fatal events were preventable highlights the need for increased focus on safety during this high-risk period from both the discharging hospital and the LTC facility. Additional studies focusing on evaluation methods to improve safe transitions for this vulnerable population should be pursued.

Bottom Line. The transition from back to LTC from hospital is a high-risk period for residents and an increased focus on safety is imperative.

Reviewer. Laura Patel, MD, Transitions LifeCare, Raleigh, NC


Development of an Advance Care Planning Program for Patients with Glioblastoma

Background. Glioblastoma has an annual incidence of ~3 per 100,000 persons.1,2 What is a feasible advance care planning (ACP) program for glioblastoma patients to be used in daily clinical practice?

Design and Participants. This study developed an ACP program and assessed the preferred content, the best time to introduce such a program in the disease trajectory, and possible barriers/facilitators for participation/implementation. A focus group (FG) with healthcare professionals (HCPs) and individual semistructured interviews with patients and proxies were conducted. Descriptive statistics were used, and interviews and FG were transcribed verbatim and analyzed thematically.

Results. The FG was 2 neurologists, a neuro-oncology nurse, an oncology nurse, 2 radiation neuro-oncologists, a hospice palliative nurse,
a general practitioner, a nursing home physician, and an end-of-life care researcher. Living patients (n=8; all had good performance status [Karnofsky Performance Status=70]) were mean±SD age 61±8 years, 75% male, and 75% highly educated (The International Standard Classification of Education); proxies of living patients (n=8) were 57±10 years, 13% male, and 25% highly educated; and proxies of deceased patients (n=5) were 68±7 years, 13% male, and 20% highly educated. All predefined topics were considered relevant by participants, including the current situation, worries/fears, (supportive) treatment options, and preferred place of care/death. Although HCPs and proxies of deceased patients indicated that the program should be implemented relatively early in the disease trajectory, patient-proxy dyads were more ambiguous. Several patient-proxy dyads indicated that the program should be initiated later in the disease trajectory. If introduced early, end-of-life topics should be postponed. A frequently mentioned participation barrier was that the program would be too confronting.

**Commentary.** This qualitative study presents facets of ACP that matter most to patients with glioblastoma, their caregivers, and healthcare providers. The most striking barrier identified by patients and caregivers is the emotional and overwhelming nature of ACP dialogues, which is echoed in previously identified challenges. Healthcare providers, in turn, fret about the previously reported fear that talking about ACP will damage their relationship with the patient. Themes identified in the study offer insight on how these barriers can be overcome. Patients and caregivers can benefit from conversations with a dedicated provider early in the disease trajectory. Navigator-led programs appear to be associated with lower rates of resource utilization near the end of life and can be accomplished with a palliative care referral. Apart from the usual disease- and prognosis-focused topics, touching on caregiver needs and financial problems also can enrich ACP conversations.

**Bottom Line.** A patient- and caregiver-centered approach is essential in building an effective ACP program for patients with glioblastoma.

**References**


**Analyzing Quality of Life and Preferences to Sustain Life in Patients in Locked-In State**

**Background.** The locked-in state (LIS) is characterized by complete immobility and anarthria while being fully conscious. What sense of well-being do patients with amyotrophic lateral sclerosis (ALS) in LIS maintain?

**Design and Participants.** This exploratory cross-sectional study interviewed patients with ALS in LIS (a Polish sample within the EU Joint Programme-Neurodegenerative Disease Research study) on well-being as a measure of psychosocial adaptation, coping mechanisms, and preferences towards life-sustaining treatments (ventilation, Percutaneous Endoscopic Gastrostomy [PEG]) and hastened death. Clinical data were recorded (ALS Functional Rating Scale-R [ALSFRS-R]), and patients completed questionnaires via eye-tracking control. In addition, caregivers judged patients’ well-being. The Kolmogorov-Smirnov test, Spearman correlation, and Mann-Whitney U test were used.

**Results.** Patients (n=19) were mean±SD age 59±9 years, 68% male, and educated mean±SD 14±3 years. Caregivers were partners=16, children=2, and professional=1. Patients judged their global quality of life in...
relation to the worst=−5 and best=+5 experiences in their own lives (The Anamnestic Comparative Self-Assessment; ≥0 indicates positive quality of life; median=1 (Q=2–3). Subjective quality of life (SEI-quality-of-life-DW;\(^3\) range=0–100, ≥50 indicates satisfactory quality of life) was median=66 (Q=58–88). Depressiveness on the ADI-12\(^4\) scored median=25 (Q=22–30; ≥28 indicates clinically relevant depression). There was no association of low quality of life/depression with time since diagnosis (r<0.03) or progression (r<0.3). The 5 patients with ALSFRS-R=0 (no extremity movement abilities and anarthria) reported positive quality of life and no depression. Information-seeking increased with time since diagnosis only (r=0.60) but no other association of coping strategies (Motor Neuron Disease Coping Scale) and clinical measures was found (r<0.3). Seventeen out of 19 would again select invasive ventilation/PEG. Patients had a median=4.5 (Q=2–7.25) wish for hastened death (Schedule of Attitudes Toward Hastened Death; range=0–20; ≥10 indicates clinically significant wish). Lastly, caregivers overestimated depressiveness (U=78, \(P=0.004\)) and underestimated quality of life (U=136, \(P=0.20\)).

Commentary. For many healthy individuals, LIS is feared to be the worst possible outcome. Despite severe physical limitations, some patients with LIS have been able to adapt to the condition and maintain a positive sense of well-being. They would often choose life-sustaining treatments and report a low desire for hastened death. Psychosocial adaptation to allow for successful coping by readjusting expectations, reframing what is important in life, and looking at things from a different perspective all helped patients maintain good quality of life. In contrast, their caregivers underestimated quality of life and overestimated depression.

Bottom Line. Contrary to public opinion, severe physical limitation does not necessarily correlate with poor quality of life. Rather, deliberate reappraisals can increase a patient’s sense of well-being.

References

Effect of Cannabinoid Use on the Clinical Characteristics of Cancer Patients

Background. There is emerging interest in the use of cannabinoids for treating various medical conditions. How does cannabinoid use affect patients’ cancer-related clinical characteristics?

Design and Participants. This retrospective review explored associations between cannabinoid use and cancer-related clinical characteristics in a cancer population. Patients in the supportive care outpatient clinic at Moffitt Cancer Center (2015-2016) completed tetrahydrocannabinol (THC) urine drug tests (UDTs) as well as same-day Edmonton Symptom Assessment Scale (ESAS) and cannabinoid history questionnaires. The ESAS (11-point rating from 0–10 [symptom absence to worst intensity]) scored previous-24-hour symptom severity, and ESAS characteristics were compared among patients with positive vs. negative test results. The Kolmogorov-Smirnov method, multiple logistic regression, and Levene’s, Mann-Whitney U, chi-square, and Fisher exact tests were used.

Results. Patients (n=332; 21% gynecologic, 15% gastrointestinal cancer) were 43% male and 52% age 50–69 years. Twenty-three percent had positive UDT results for THC. Differences were seen between THC-positive and THC-negative patients for age (median=52 [lower quartile=44; upper quartile=56] vs. 58 [48; 67] years; \(P<0.001\)), male sex (54% vs. 40%; \(P=0.034\)), and past/current cannabinoid use (66% vs. 26%; \(P<0.001\)). THC-positive (vs. THC-negative) patients had higher scores for pain (7 [lower quartile=5; upper quartile=8] vs. 5 [3; 7]; \(P=0.001\)), nausea (1 [0; 3] vs. 0 [0; 3]; \(P=0.049\)), appetite (4 [2; 7] vs. 3 [0; 5.75]; \(P=0.015\)), overall well-being (5.5 [4; 7] vs. 5 [3; 6]; \(P=0.002\)), spiritual well-being (5 [2; 6] vs. 3 [1; 3]; \(P=0.015\)), insomnia (7
Commentary. There exists tremendous public interest and widespread use of medical cannabis among patients with cancer. In this retrospective review, researchers at the NCI-Designated Cancer Center have analyzed charts of patients in an outpatient supportive care clinic. Almost one-fourth of the patients’ UDTs were positive for THC metabolites, which is consistent with prior research. These patients were more likely to be young and male and reported more frequent cannabis use. Interestingly, the patients also self-reported a higher severity of pain, nausea, insomnia, and worse overall and spiritual well-being compared with patients whose urine was negative for THC. Many potential reasons could explain the findings; however, it seems likely that it was the inadequate control of symptoms that led to the use of cannabis. Therefore, inquiring about the use and motivations behind cannabis use seems crucial for palliative care clinicians taking care of patients with cancer.

Bottom Line. Use of medical cannabis among cancer patients may be related to suboptimal symptom control.

References

Rave Reviews
Given the paucity of palliative care pediatricians, many “adult” clinicians will find themselves caring for children at some point. This eminently practical article highlights some of the major differences between adult and pediatric palliative care, with helpful advice about how to care for children.

In pediatrics, we care for the child as well as the family. This is a fabulous overview of how to support parents of seriously ill patients in communicating openly and honestly with their children.
The longer an adult stays in the intensive care unit (ICU), the worse their prognosis; however, in pediatrics (especially neonatology), it’s exactly the opposite. This article helps guide clinicians through the unique worlds of the pediatric and neonatal ICUs, equipping them with necessary tools to care for critically ill children.

PC-FACS Feedback
We appreciate your feedback. Help us help you—send your comments to pc-facs@aaahpm.org.

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