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Clinical Update: Literature Abstracts

MEASURES

Development of a Symptom Assessment Instrument for Chronic Hemodialysis Patients: The Dialysis Symptom Index

Weisbord, S., Fried, L., Arnold, R., Rotondi, A., Fine, M., Levenson, D., and Switzer, G.

Journal of Pain and Symptom Management, 27 (2004), 226–240

Little is known about the prevalence, severity, or impact of symptoms in hemodialysis patients because of the lack of a validated symptom assessment instrument. We systematically developed an index to assess physical and emotional symptom burden in this patient population. We employed four steps in the generation of this index: a review of dialysis quality-of-life instruments, three focus groups, experts' content validity assessment, and test–retest reliability measurement. Seventy-five symptoms were identified. Of these, 46 appeared in four or more of the instruments/focus groups and were considered for inclusion. Twelve were grouped into other symptom constructs, and experts judged four of the remaining items not to be pertinent, leaving 30 items in the new index. Overall kappa statistic was 0.48 ± 0.22. These steps allowed the systematic development of a 30-item symptom assessment index for hemodialysis patients. Additional reliability and validity testing is needed prior to its widespread use.

Instrument for Detection of Delirium in General Hospitals: Adaptation of the Confusion Assessment Method

González, M., de Pablo, J., Fuente, E., Valdés, M., Peri, J.M., Nomdedeu, M., and Matrai, S.

Psychosomatics, *45* (2004), 426–431

Delirium is a common and severe disorder that is often misdiagnosed. The use of screening instruments is advisable for its early detection and treatment. In this study, the authors present an adaptation of the Confusion Assessment Method in order to improve its psychometric properties. One hundred fifty-three elderly inpatients were assessed in a four-phase procedure. Interrater reliability was high (kappa = 0.89). Sensitivity was 90%, and specificity was 100%; the value for negative predictive accuracy was 97%, and the value for positive predictive accuracy was 100%. The adaptation has convergent agreement with two other mental status tests, the Mini-Mental Status Examination and the Delirium Rating Scale. Our results suggest that the adaptation of the Confusion Assessment Method is sensitive, specific, reliable, and easy to use by clinicians.

A Comparison of Five Pain Assessment Scales for Nursing Home Residents with Varying Degrees of Cognitive Impairment

Closs, S., Barr, B., Briggs, M., Cash, K., and Seer, K.

Journal of Pain and Symptom Management, *27* (2004), 196–205

The aim of the study was to compare five different pain assessment scales for use with people with different levels of cognitive impairment who resided in nursing homes. The verbal rating scale, horizontal numeric rating scale, Faces pictorial scale, color analogue scale, and mechanical visual analogue scale were presented in random order to 113 residents. Cognitive impairment was assessed using the Mini-Mental State Examination. The use of the verbal rating scale was the most successful with this group, completed by 80.5% overall, and 36% of those with severe cognitive impairment. Repeated explanation improved completion rates for all the scales. Consistency between scores on the five scales was good for those with no to moderate cognitive impairment and poor for those severely impaired. This study showed no difference in pain scores according to cognitive status.

The CARES-SF Used for Prospective Assessment of Health-Related Quality of Life after Stem Cell Transplantation

Hjermstad, M., Evensen, S., Kvaløy, S., Loge, J., Fayers, P., and Kaasa, S.

Psycho-Oncology, *12* (2003), 803–813

By employing the Cancer Rehabilitation and Evaluation System short form (CARES-SF) prospectively we wanted to focus on rehabilitation needs after high-dose chemotherapy (HDC) and stem cell transplantation to identify problems that should be addressed by health care professionals during the course of disease and treatment. The CARES-SF was administered before and at 2, 6, and 12 months posttransplant to 130 cancer patients treated with HDC and allogeneic (SCT) or autologous stem cell transplantation (ASCT). Physical function scale scores were compared with the corresponding scale of the EORTC QLQ-C30. The SCT group reported significantly better physical function than the ASCT group before transplant on both the CARES-SF ($p < 0.0001$) and the EORTC QLQ-C30 ($p < 0.01$). Almost identical mean CARES-SF scores across groups (SCT: 0.7–1.4, ASCT: 0.8–1.3) were found at the subsequent assessments, consistent with the QLQ-C30 data. Correlations between CARES-SF and QLQ-C30 Physical Function Scales ranged from 0.45 to 0.65. The SCT group had better psychosocial subscale scores (mean 0.4 and 0.5 vs. ASCT: 0.7 and 0.8, $p < 0.01$) at the 6- and 12-month assessments, as well as better satisfaction on the marital subscale ($p = 0.01$) 6 months posttransplant. Few patients requested specific help: 19% at baseline with "fear of the cancer progressing" and 9% with "reduction in physical energy" after 6 and 12 months. The CARES-SF detected differences across groups of patients as well as within-patient changes over time. The possibility for patients to express their need for professional assistance renders the CARES-SF appropriate after SCT/ASCT. The sexual, marital, and medical interaction subscales in particular address specific issues of relevance for follow-up care, compared with more traditional questionnaires assessing health-related quality of life.

Validation of a Symptom Measure Suitable for Use among Palliative Care Patients in the Community: CAMPAS-R

Ewing, G., Todd, C., Rogers, M., Barclay, S., and McCabe, J.

Journal of Pain and Symptom Management 27 (2004), 287–299

The purpose of the study was to investigate psychometric properties of CAMPAS-R, an instrument for prospectively monitoring patients' symptoms and needs during palliative care at home. CAMPAS-R was piloted for face and content validity and then administered alongside criterion measures to a home care sample. Cronbach's alpha was used to test internal consistency, and criterion-related validity was tested by nonparametric correlation with the Brief Pain Inventory (BPI), Hospital Anxiety and Depression Scale (HADS), and EORTC QLQ-C30. Predictive validity was assessed by relating CAMPAS-R scores to survival. One hundred and nine patients were recruited to the study. Good reliability and high correlations between CAMPAS-R and criterion measures were found. Predictive validity was demonstrated by significant differences in symptom scores between groups differing in length of survival. CAMPAS-R is acceptable to patients, families, and primary care professionals and is a valid, reliable instrument, which has the benefit of being easy to score.

A Patient–Doctor Relationship Questionnaire (PDRQ-9) in Primary Care: Development and Psychometric Evaluation

Van der Feltz-Cornelis, C., Van Oppen, P., Van Marwijk, H., De Beurs, E., and Van Dyck, R.

General Hospital Psychiatry 26 (2004), 115–120

In health care research, the patient–doctor relationship as perceived by the patient is considered important. Our aim was to develop and validate a questionnaire that assesses the patient–doctor relationship, the Patient–Doctor Relationship Questionnaire (PDRQ-9). The PDRQ-9 was developed out of the Helping Alliance Questionnaire of Luborsky, a scale that measures the therapeutic alliance in psychotherapy. Its psychometric qualities and validity in general practice were assessed, with the collaboration of 110 general practice patients and 55 patients in an epilepsy clinic. Principal components analysis demonstrates a two-factorial structure, one related to the doctor and one related to the medical symptoms of the patient. Both show high reliability but as the second factor explains only 9% of the variance, it is eliminated from the questionnaire. The PDRQ-9 provides researchers a brief measure of the therapeutic aspects of the patient–doctor relationship in the primary care setting. It is a valuable tool for scientific and practical purposes involving the monitoring of the patient–doctor relationship.

SYMPTOM CONTROL

Increased Family Reports of Pain or Distress in Dying Oregonians: 1996 to 2002

Fromme, E., Tilden, V., Drach, L., and Tolle, S.

Journal of Palliative Medicine, *7* (2004), 431–442

The aim of this study was to compare the prevalence of family-reported pain or distress during the last week of decedents' lives during two times: November 1996 to December 1997 and June 2000 to March 2002. We telephone-surveyed family caregivers of Oregonians who had died 2 to 5 months previously in private homes, nursing homes, and other community-based settings. Caregivers were asked to rate the level of pain or distress during the decedent's final week of life on a four-point scale. Data were collected from 340 respondents from 1996 to 1997 and 1384 respondents from 2000 to 2002. We found that the prevalence of family-reported moderate or severe pain or distress (compared to comfortable or mild pain or distress) in Oregon decedents increased from 30.8% in 1996–1997 to 48% in 2000–2002. Using a logistic regression model to control for differences between the two sampling times and other predictors of increased pain or distress, decedents in 2000–2002 remained approximately twice as likely to be reported to be in moderate or severe pain or distress during the last week of their lives (Time 2 vs. Time 1, odds ratio [OR] 2.09, 95% confidence interval [CI] 1.59–2.74). We discuss possible explanations for this finding, including media effect created by the publicity surrounding the second ballot measure and subsequent availability of physician-assisted suicide in November 1997. Alternatively, trends in underfunding and understaffing of hospice and community nursing resources may have disproportionately affected care in the final week of life, which depends heavily on skilled nursing care for effective symptom control and psychosocial support of the patient and family.

No Evidence for Sex Differences in the Severity and Treatment of Cancer Pain

Edrington, J., Paul, S., Dodd, M., West, C., Facione, N., Tripathy, D., Koo, P., Schumacher, K., and Miaskowski, C.

Journal of Pain and Symptom Management, *28* (2004), 225–232

Although chronic pain is experienced by ~50–90% of patients with metastatic cancer, little is known about sex differences in chronic cancer pain. Therefore, the purposes of this study, in a sample of oncology outpatients ($n = 187$) who were experiencing pain from bone metastasis, were (1) to determine if there were sex differences in various pain characteristics, including pain intensity, and (2) to determine if there were sex differences in the prescription and consumption of analgesic medications. No significant sex differences were found in any of the baseline pain characteristics. In addition, no significant sex differences were found in analgesic prescriptions or intake of analgesic medications. Of note, men reported significantly higher pain interference scores for sexual activity than women. The study findings are important because they suggest that, unlike in acute pain, sex may not influence patients' perceptions of and responses to chronic cancer pain.

Methadone versus Morphine as a First-Line Strong Opioid for Cancer Pain: A Randomized, Double-Blind Study

Bruera, E., Palmer, J.L., Bosnjak, S., Rico, M.A., Moyano, J., Sweeney, C., Strasser, F., Willey, J., Bertolino, M., Mathias, C., Spruyt, O., and Fisch, M.

Journal of Clinical Oncology, *22* (2004), 185–192

The objective was to compare the effectiveness and side effects of methadone and morphine as first-line treatment with opioids for cancer pain. Patients in international palliative care clinics with pain requiring initiation of strong opioids were randomly assigned to receive methadone (7.5 mg orally every 12 h and 5 mg every 4 h as needed) or morphine (15 mg sustained release every 12 h and 5 mg every 4 h as needed). The study duration was 4 weeks. A total of 103 patients were randomly assigned to treatment (49 in the methadone group and 54 in the morphine group). The groups had similar baseline scores for pain, sedation, nausea, confusion, and constipation. Patients receiving methadone had more opioid-related drop-outs (11 of 49; 22%) than those receiving morphine (3 of 54; 6%; $p = 0.019$). The opioid escalation index at days 14 and 28 was similar between the two groups. More than three-fourths of patients in each group reported a 20% or more reduction in pain intensity by day 8. The proportion of patients with a 20% or more improvement in pain at 4 weeks in the methadone group was 0.49 (95% CI, 0.34–0.64) and was similar in the morphine group (0.56; 95% CI, 0.41–0.70). The rates of patient-reported global benefit were nearly identical to the pain response rates and did not differ between the treatment groups. Methadone did not produce superior analgesic efficiency or overall tolerability at 4 weeks compared with morphine as a first-line strong opioid for the treatment of cancer pain.

The Prevalence, Key Causes, and Management of Insomnia in Palliative Care Patients

Hugel, H., Ellershaw, J., Cook, L., Skinner, J., and Irvine, C.

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In a prospective audit, the prevalence, key causes, and treatment of insomnia prior to admission were evaluated in a population of hospice patients using a questionnaire based on a review article of key features related to insomnia in the palliative care setting. Seventy-four patients completed the questionnaire. Fifty-two (70%) patients had insomnia symptoms. Uncontrolled physical symptoms, most often pain (15 patients), was the commonest cause of insomnia, cited by 31 (60%) sleep-disturbed patients. Thirteen (62%) of 21 patients who had been prescribed hypnotic medication reported an improvement with the prescribed medication. Twenty (38%) of the 52 patients with insomnia suggested that improved symptom control would improve their sleep, and only two (4%) suggested the need for more hypnotic medication. We conclude that insomnia is a common symptom in terminally ill patients and that improved symptom control should be a priority in the management of insomnia in this group of patients.

Amantadine for Executive Dysfunction Syndrome in Patients with Dementia

Drayton, S., Davies, K., Steinberg, M., Leroi, I., Rosenblatt, A., and Lyketsos, C.

Psychosomatics, *45* (2004), 205–209

This article reports the results of an open uncontrolled chart review study of amantadine treatment for executive dysfunction syndrome in patients with dementia. All patients admitted to the neuropsychiatry or geriatric psychiatry inpatient units of Johns Hopkins Hospital in 2000 and 2001 who were treated empirically with amantadine for executive dysfunction syndrome were included in the review. Of the 30 patients whose cases were reviewed, 17 (57%) were at least "much improved," and most patients were discharged taking amantadine, suggesting that their physicians believed that they may have benefited from it. The medication was well tolerated in this frail group of patients. Most patients were taking one or more concurrent psychotropic medications, which may have contributed to the positive outcomes. Despite its limitations, this study offers preliminary data to support a controlled trial of amantadine in patients with executive dysfunction syndrome.

Pilot Evaluation of Mirtazapine for the Treatment of Hot Flashes

Perez, D., Loprinzi, C., Barton, D., Pockag, B., Sloan, J., Novotny, P., and Christensen, B.

The Journal of Supportive Oncology, *2* (2004), 50–56

This prospective, single-arm, pilot clinical trial, developed to evaluate the efficacy and tolerability of mirtazapine for alleviating hot flashes, was conducted between May 2001 and January 2002. Patients' baseline characteristics were collected during the first week of the study. At the beginning of the second week, patients were started on mirtazapine at a dose of 7.5 mg at bedtime. The dose of mirtazapine was then increased to 15 mg at week 3 and to 30 mg at week 4. For week 5, patients could choose whether to take 15 mg/d or 30 mg/d. Data were obtained primarily from patient-completed questionnaires. Data from 22 evaluable women were available. For the 16 patients who completed the study, the median reductions in total daily hot flashes and weekly hot-flash scores from their baselines were 52.5% and 59.5%, respectively. Patients reported improvements in tension, trouble sleeping, abnormal sweating, distress from hot flashes, satisfaction with hot-flash control, overall quality of life, and impact of hot flashes on quality of life. Patients also reported increases in appetite and dry mouth. Although data from a double-blind, placebo-controlled clinical trial would be necessary to more definitively elucidate the efficacy and toxicity of mirtazapine in patients with hot flashes, the available data suggest that mirtazapine is a reasonable treatment to consider in patients with hot flashes, particularly in those with anxiety and sleep disturbances.

Intrathecal Ziconotide in the Treatment of Refractory Pain in Patients with Cancer or AIDS

Staats, P., Yearwood, T., Charapata, S., Presley, R., Wallace, M., Byas-Smith, M., Fischer, R., Bryce, D., Mangieri, E., Luther, R., Mayo, M., McGuire, D., and Ellis, D.

JAMA, *291* (2004), 63–70

Ziconotide (formerly SNX-111) selectively blocks N-type voltage-sensitive calcium channels and may be effective in patients with pain that is refractory to opioid therapy or those with intolerable opioid-related adverse effects. Our objective was to assess the safety and efficacy of intrathecal ziconotide in patients with pain that is refractory to conventional treatment. A double-blind, placebo-controlled, randomized trial was conducted from March 12, 1996, to July 11, 1998, at 32 study centers in the United States, Australia, and the Netherlands. Patients were 111 individuals ages 24 to 85 years with cancer or AIDS and a mean Visual Analog Scale of Pain Intensity (VASPI) score of 50 mm or greater. Patients were randomly assigned in a 2:1 ratio to receive ziconotide or placebo treatment. Intrathecal

ziconotide was titrated over 5 to 6 days, followed by a 5-day maintenance phase for responders and crossover of nonresponders to the opposite treatment group. Mean percentage change in VASPI score from baseline to the end of the initial titration period was analyzed. Of the evaluable population, 67 (98.5%) of 68 patients receiving ziconotide and 38 (95%) of 40 patients receiving placebo were taking opioids at baseline (median morphine equivalent dosage of 300 mg/d for the ziconotide group and 600 mg/d for the placebo group; P = 0.63, based on mean values), and 36 had used intrathecal morphine. Mean (*SD*) VASPI scores were 73.6 (1.8) mm in the ziconotide group and 77.9 (2.3) mm in the placebo group ($p = 0.18$). Mean VASPI scores improved 53.1% (95% confidence interval [CI], 44.0%–62.2%) in the ziconotide group and 18.1% (95% CI, 4.8%–31.4%) in the placebo group ($p < 0.001$), with no loss of efficacy of ziconotide in the maintenance phase. Pain relief was moderate to complete in 52.9% of patients in the ziconotide group compared with 17.5% in the placebo group (P < 0.001). Five patients receiving ziconotide achieved complete pain relief, and 50.0% of patients receiving ziconotide responded to therapy compared with 17.5% of those receiving placebo ($p = 0.001$). Intrathecal ziconotide provided clinically and statistically significant analgesia in patients with pain from cancer or AIDS.

Massage Therapy for Symptom Control: Outcome Study at a Major Cancer Center

Cassileth, B. and Vickers, A.

Journal of Pain and Symptom Management, *28* (2004), 244–249

Massage is increasingly applied to relieve symptoms in patients with cancer. This practice is supported by evidence from small randomized trials. No study has examined massage therapy outcome in a large group of patients. At Memorial Sloan-Kettering Cancer Center, patients report symptom severity pre- and postmassage therapy using 0–10 rating scales of pain, fatigue, stress/anxiety, nausea, depression, and "other." Changes in symptom scores and the modifying effects of patient status (in- or outpatient) and type of massage were analyzed. Over a 3-year period, 1,290 patients were treated. Symptom scores were reduced by approximately 50%, even for patients reporting high baseline scores. Outpatients improved about 10% more than inpatients. Benefits persisted, with outpatients experiencing no return toward baseline scores throughout the duration of 48-h follow-up. These data indicate that massage therapy is associated with substantive improvement in cancer patients' symptom scores.

The Effects of Pharmacologically Induced Hypogonadism on Mood in Healthy Men

Schmidt, P., Berlin, K., Danaceau, M., Neeren, A., Haq, N., Roca, C., and Rubinow, D.

Archives of General Psychiatry, *61* (2004), 997–1004

The effects of declining androgen secretion on mood regulation and the potential psychotropic efficacy of androgen replacement in men are largely undetermined. To examine the effects on mood of the acute suppression of testosterone secretion, a double-blind, placebo-controlled, crossover (self-as-own-control) study was conducted at an ambulatory care clinic in a research hospital.

Participants were 31 healthy adult men with no history of psychiatric illness or substance or anabolic steroid abuse. Men received depot leuprolide acetate (Lupron, 7.5 mg intramuscularly) every 4 weeks for 3 months. After the first month of Lupron alone, all men received (in addition to Lupron) testosterone enanthate (200 mg intramuscular) or placebo (sesame oil as color-matched vehicle) every 2 weeks for 1 month each in a crossover design. The order of administration of testosterone and placebo was randomly assigned and counterbalanced. Mood and behavior rating scores (self-report and rater administered) were analyzed. With the exceptions of hot flushes, libido, and the feeling of being emotionally charged, none of the symptoms measured showed a significant difference across eugonadal, Lupron plus placebo, and Lupron plus testosterone conditions. Despite the absence of a uniform effect of Lupron plus placebo on mood, three men experienced clinically relevant mood symptoms during this induced hypogonadal condition. High baseline levels of sexual functioning predicted the greatest decline in sexual function during Lupron plus placebo. These data, the first to describe the effects on mood of induced hypogonadism in healthy young men, suggest that short-term hypogonadism is sufficient to precipitate depressive symptoms in only a small minority of younger men. The predictors of this susceptibility remain to be determined.

Growth Hormone–Releasing Hormone in HIV-Infected Men with Lipodystrophy: A Randomized Controlled Trial

Koutkia, P., Canavan, B., Breu, J., Torriani, M., Kissko, J., and Grinspoon, S.

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Reduced growth hormone (GH) concentrations are observed in men with human immunodeficiency virus (HIV) lipodystrophy. *Objective:*To investigate the effects of growth hormone–releasing hormone (GHRH), a GH secretagogue, in treatment of HIV lipodystrophy. Randomized, double-blind, placebo-controlled trial conducted at a research center in the United States between October 2002 and June 2003 and enrolling 31 HIV-infected men aged 18 to 60 years with evidence of lipodystrophy. Participants were assigned to receive GHRH (1 mg subcutaneously twice daily) or placebo for 12 weeks. The primary outcome was change in concentrations of insulin-like growth factor 1 (IGF-1) to detect overall change in GH levels in response to GHRH. Secondary end points included body composition by dual-energy x-ray absorptiometry and computed tomography, lipodystrophy ratings, and levels of glucose, insulin, and lipids. Mean (*SD*) IGF-1 concentrations increased significantly in the GHRH group versus the placebo group (104 [110] ng/mL vs. 6 [44] ng/mL, P = 0.004). Lean body mass significantly increased in the GHRH group versus the placebo group (0.9 [1.3] kg vs. −0.3 [1.7] kg, P = 0.04), trunk fat significantly decreased (−0.4 [0.7] kg vs. 0.2 [0.6] kg, $p = 0.03$), and the ratio of trunk to lower extremity fat improved significantly (−0.22 [0.32] vs. 0.14 [0.29], $p = 0.005$). Abdominal visceral fat was reduced (−19.2 [36.6] cm^2 vs. 2.3 [24.3] cm^2, $p = 0.07$) and the ratio of abdominal visceral fat to abdominal subcutaneous fat improved significantly more in the GHRH group (−0.19 [0.28] vs. 0.07 [0.27], $p = 0.02$). Both physician and patient rating of lipodystrophy in the arms, legs, and abdomen also improved significantly. Levels of glucose, insulin, and lipids did not change significantly. GHRH was well tolerated and effectively increased levels of IGF-1 in HIV-infected men with lipodystrophy. Total and regional body composition improved in response to GHRH, with increased lean mass and reduced truncal and visceral fat. Use of GHRH may potentially be a beneficial treatment strategy for this population.

Effect of Galantamine Hydrobromide in Chronic Fatigue Syndrome: A Randomized Controlled Trial

Blacker, R., Greenwood, D., Wesnes, K., Wilson, R., Woodward, C., Howe, I., and Ali, T.

JAMA, *292* (2004), 1195–1204

There is no established pharmacological treatment for the core symptoms of chronic fatigue syndrome (CFS). Galantamine hydrobromide, an acetyl cholesterone inhibitor, has pharmacological properties that might benefit patients with CFS. The study's objective was to compare the efficacy and tolerability of galantamine hydrobromide in patients with CFS. Randomized, double-blind trial conducted June 1997 through July 1999 at 35 outpatient centers in the United Kingdom ($n = 17$), United States ($n = 14$), the Netherlands ($n = 2$), Sweden ($n = 1$), and Belgium ($n = 1$) involving 434 patients with a clinical diagnosis of CFS (modified U.S. Centers for Disease Control and Prevention criteria). A total of 89 patients were randomly assigned to receive 2.5 mg of galantamine hydrobromide; 86 patients, 5.0 mg; 91 patients, 7.5 mg; and 86 patients, 10 mg (these patients received medicine in the tablet form 3 times per day); a total of 82 patients received matching placebo tablets 3 times per day. The primary efficacy variable was the global change on the Clinician Global Impression Scale after 4, 8, 12, and 16 weeks of treatment. Secondary outcomes were changes in core symptoms of CFS on the Chalder Fatigue Rating Scale, the Fibromyalgia Impact Questionnaire, and the Pittsburgh Sleep Quality Index; changes in quality of life on the Nottingham Health Profile; and assessment of plasma-free cortisol levels and cognitive performance on a computer-based battery of tests. After 16 weeks, there were no statistically significant differences between any of the galantamine or placebo groups in clinical condition on the Clinician Global Impression Scale, or for any of the secondary end points. Exploratory regression analysis failed to detect any consistent prognostic factor that might have influenced the primary or any secondary outcome measures. This trial did not demonstrate any benefit of galantamine over placebo in the treatment of patients with CFS.

PSYCHOSOCIAL INTERVENTION

Psychological, Behavioral, and Immune Changes after a Psychological Intervention: A Clinical Trial

Anderson, B., Farrar, W., Golden-Kreutz, D., Glaser, R., Emery, C., Crespin, T., Sharpiro, C., and Carson, W.

This randomized clinical trial tests the hypothesis that a psychological intervention can reduce emotional distress, improve health behaviors and dose intensity, and enhance immune responses. We studied 227 women who were surgically treated for regional breast cancer. Before adjuvant therapy, women completed interviews and questionnaires assessing emotional distress, social adjustment, and

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health behaviors. A 60-ml blood sample was drawn for immune assays. Patients were randomly assigned to either the intervention group or assessment only group. The intervention was conducted in small patient groups, with one session per week for 4 months. The sessions included strategies to reduce stress, improve mood, alter health behaviors, and maintain adherence to cancer treatment and care. Reassessment occurred after completion of the intervention. As predicted, patients receiving the intervention showed significant lowering of anxiety, improvements in perceived social support, improved dietary habits, and reduction in smoking (all $p < 0.05$). Analyses of adjuvant chemotherapy dose intensity revealed significantly more variability (i.e., more dispersion in the dose-intensity values) for the assessment arm ($p < 0.05$). Immune responses for the intervention patients paralleled their psychological and behavioral improvements. T-cell proliferation in response to phytohemagglutinin and concanavalin A remained stable or increased for the intervention patients, whereas both responses declined for assessment patients; this effect was replicated across three concentrations for each assay (all $p < 0.01$). These data show a convergence of significant psychological, health behavior, and biologic effects after a psychological intervention for cancer patients.

Ethical Wills and Suffering in Patients with Cancer: A Pilot Study

Gessert, C., Baines, B., Kuross, S., Clark, C., and Haller, I.

Suffering at the end of life may be caused by many factors, including pain and other symptoms, concern about family and friends, and loss of control of one's life. Several authors have suggested that loss of meaning is pivotal in suffering. An ethical will (EW) is a statement, usually written, capturing one's values, wisdom, hopes, and advice. EWs have been suggested as a vehicle for finding meaning as the end of life approaches. This pilot study of EWs examined methods for exploring the role of EWs in reducing suffering at the end of life. Oncology clinic patients 65+ years of age in active therapy for cancer were randomly assigned to one of two arms: EW or control. Subjects in both arms had writing assignments, three home visits, and exit interviews. Suffering was measured at baseline and at the time of the exit interview, using a series of Likert-like scales. Twenty-four subjects (10 EW and 14 control) completed the study. Among EW subjects, trends toward reduced suffering were noted in "concern for loved ones," "unfinished business," and "fear of the future." Several methodological issues were identified by this pilot study, including selection of population for studying suffering, placebo effect, and randomization. EW may be valuable in alleviating suffering; a larger study will be needed to examine efficacy. The study of interventions designed to reduce suffering at the end of life requires careful attention to the definition and measurement of suffering, study design, and subject selection.

Fluoxetine, Cognitive-Behavioral Therapy, and Their Combination for Adolescents with Depression Treatment for Adolescents with Depression Study (TADS) Randomized Controlled Trial

March, J., Silva, S., Petrycki, S., Curry, J., Wells, K., Fairbank, J., Burns, B., Domino, M., and McNulty, S.

JAMA, *292* (2004), 807–820

Initial treatment of major depressive disorder in adolescents may include cognitive-behavioral therapy (CBT) or a selective serotonin reuptake inhibitor (SSRI). However, little is known about their relative or combined effectiveness. The study's objective was to evaluate the effectiveness of four treatments among adolescents with major depressive disorder. We conducted a randomized controlled trial of a volunteer sample of 439 patients between the ages of 12 and 17 years with a primary *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnosis of major depressive disorder. The trial was conducted at 13 U.S. academic and community clinics between spring 2000 and summer 2003. The intervention consisted of 12 weeks of (1) fluoxetine alone (10 to 40 mg/d), (2) CBT alone, (3) CBT with fluoxetine (10 to 40 mg/d), or (4) placebo (equivalent to 10 to 40 mg/d). Placebo and fluoxetine alone were administered double-blind; CBT alone and CBT with fluoxetine were administered unblinded. Main outcome measures included: Children's Depression Rating Scale-Revised total score and, for responder analysis, a (dichotomized) Clinical Global Impressions improvement score. Compared with placebo, the combination of fluoxetine with CBT was statistically significant ($p = 0.001$) on the Children's Depression Rating Scale-Revised. Compared with fluoxetine alone ($p = 0.02$) and CBT alone ($p = 0.01$), treatment of fluoxetine with CBT was superior. Fluoxetine alone is a superior treatment to CBT alone ($p = 0.01$). Rates of response for fluoxetine with CBT were 71.0% (95% confidence interval [CI], 62%–80%), fluoxetine alone, 60.6% (95% CI, 51%–70%), CBT alone, 43.2% (95% CI, 34%–52%), and

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placebo, 34.8% (95% CI, 26%–44%). On the Clinical Global Impressions improvement responder analysis, the two fluoxetine-containing conditions were statistically superior to CBT and to placebo. Clinically significant suicidal thinking, which was present in 29% of the sample at baseline, improved significantly in all four treatment groups. Fluoxetine with CBT showed the greatest reduction ($p = 0.02$). Seven (1.6%) of 439 patients attempted suicide; there were no completed suicides. The combination of fluoxetine with CBT offered the most favorable trade-off between benefit and risk for adolescents with major depressive disorder.

Telephone Psychotherapy and Telephone Care Management for Primary Care Patients Starting Antidepressant Treatment: A Randomized Controlled Trial

Simon, G., Ludman, E., Tutty, S., Operskalski, B., and Von Korff, M.

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Both antidepressant medication and structured psychotherapy have been proven efficacious, but less than one-third of people with depressive disorders receive effective levels of either treatment. The objective of the study was to compare usual primary care for depression with two intervention programs: telephone care management and telephone care management plus telephone psychotherapy. The design was a three-group randomized controlled trial with allocation concealment and blinded outcome assessment conducted between November 2000 and May 2002. A total of 600 patients beginning antidepressant treatment for depression were systematically sampled from seven group-model primary care clinics; patients already receiving psychotherapy were excluded. The interventions included: Usual primary care; usual care plus a telephone care management program including at least three outreach calls, feedback to the treating physician, and care coordination; usual care plus care management integrated with a structured eight-session cognitive-behavioral psychotherapy program delivered by telephone. Main outcome measures include: Blinded telephone interviews at 6 weeks, 3 months, and 6 months assessed depression severity (Hopkins Symptom Checklist Depression Scale and the Patient Health Questionnaire), patient-rated improvement, and satisfaction with treatment. Computerized administrative data examined use of antidepressant medication and outpatient visits. Treatment participation rates were 97% for telephone care management and 93% for telephone care management plus psychotherapy. Compared with usual care, the telephone psychotherapy intervention led to lower mean Hopkins Symptom Checklist Depression Scale depression scores ($p = 0.02$), a higher proportion of patients reporting that depression was "much improved" (80% vs. 55%, $p < 0.001$), and a higher proportion of patients "very satisfied" with depression treatment (59% vs. 29%, $p < 0.001$). The telephone care management program had smaller effects on patient-rated improvement (66% vs. 55%, $p = 0.04$) and satisfaction (47% vs. 29%, $p = 0.001$); effects on mean depression scores were not statistically significant. For primary care patients beginning antidepressant treatment, a telephone program integrating care management and structured cognitive-behavioral psychotherapy can significantly improve satisfaction and clinical outcomes. These findings suggest a new public health model of psychotherapy for depression including active outreach and vigorous efforts to improve access to and motivation for treatment.

Antidepressants and the Risk of Suicidal Behaviors

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The relation between use of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), and suicidal ideation and behaviors has received considerable public attention recently. The use of such drugs among teenagers has been of particular concern. The objective of the study was to estimate the relative risks (RRs) of nonfatal suicidal behavior in patients starting treatment with one of three antidepressant drugs compared with patients starting treatment with dothiepin. The design of the study was a matched case-control study of patients treated in U.K. general practices using the U.K. General Practice Research Database for 1993–1999. The base population included 159,810 users of the four antidepressant drugs. Participants could have used only one of these antidepressants and had to have received at least one prescription for the study antidepressant within 90 days before their index date (the date of suicidal behavior or ideation for cases and the same date for matched controls). The main outcome measures included: Frequency of first-time exposure to amitriptyline, fluoxetine, paroxetine, and dothiepin of patients with a recorded diagnosis of first-time nonfatal suicidal behavior or suicide compared with comparable patients who did not exhibit suicidal behavior. After controlling for age, sex, calendar time, and time from first antidepressant prescription to the onset of suicidal behavior, the relative

risks for newly diagnosed nonfatal suicidal behavior in 555 cases and 2062 controls were 0.83 (95% confidence interval, [CI] 0.61–1.13) for amitriptyline, 1.16 (95% CI, 0.90–1.50) for fluoxetine, and 1.29 (95% CI, 0.97–1.70) for paroxetine compared with those using dothiepin. The RR for suicidal behavior among patients first prescribed an antidepressant within 1 to 9 days before their index date was 4.07 (95% CI, 2.89–5.74) compared with patients who were first prescribed an antidepressant 90 days or more before their index date. Time since first antidepressant prescription was not, however, a confounder of the relation between specific antidepressants and suicidal behavior, as its relation to suicidal behavior was not materially different among users of the four study drugs. Similarly for fatal suicide, the RR among patients who were first prescribed an antidepressant within 1 to 9 days before their index date was 38.0 (95% CI, 6.2–231) compared with those who were first prescribed an antidepressant 90 days or more before their index date. There were no significant associations between the use of a particular study antidepressant and the risk of suicide. The risk of suicidal behavior after starting antidepressant treatment is similar among users of amitriptyline, fluoxetine, and paroxetine compared with the risk among users of dothiepin. The risk of suicidal behavior is increased in the first month after starting antidepressants, especially during the first 1 to 9 days. A possible small increase in risk (bordering statistical significance) among those starting the newest antidepressant, paroxetine, is of a magnitude that could readily be due to uncontrolled confounding by severity of depression. Based on limited information, we also conclude that there is no substantial difference in effect of the four drugs on people aged 10 to 19 years.