Effect of Sex and Gender on Drug-Seeking Behavior During Invasive Medical Procedures[1]

Verena J. Stinshoff, BS, Elvira V. Lang, MD, Kevin S. Berbaum, PhD, Susan Lutgendorf, PhD, Henrietta Logan, PhD
Michael Berbaum, PhD

Rationale and Objectives. To assess how sex affects patients' drug-seeking, pain, and anxiety during interventional procedures.

Materials and Methods. Data from 159 patients were derived from two control groups of a prospective randomized trial. Seventy-six patients were male, 83 female. Patients in the standard group (n = 79) received the standard care typical for the institution; patients in the attention group (n = 80) had an additional empathic provider who stayed with them throughout the procedure. All patients were asked every 15 minutes to rate their pain and anxiety on 0–10 self-rating scales. All had access to intravenous sedatives and narcotics through a patient-controlled analgesia model. Univariate analysis of variance with a between-patient factor for group and another between-patient factor for sex was used.

Results. There was a significant interaction between group attribution and sex with regard to drug request and pain and anxiety ratings. Patients in the attention group requested significantly fewer drugs than patients in the standard group. Men asked for more drugs than women under standard care, but for less in the attention group. Pain and anxiety ratings for women were significantly lower in the attention group compared with standard treatment, but for men, there was no significant difference.

Conclusion. Although both men and women benefit from the presence of an empathic provider during invasive medical procedures, men benefit more in terms of medication reduction, whereas women benefit more in terms of pain and anxiety reduction. Awareness of these gender-specific differences can aid in formulation of patient-specific treatment plans.

Key Words. Sex; drugs; treatment; analgesics.

It is generally accepted that men and women exhibit important differences in their experiences of pain and anxiety (1,2) and tend to resort to gender-specific coping strategies (2). Studies have shown that men and women differ in their sensitivity toward painful stimuli, their physiologic response, and in their metabolism of analgesics and sedatives administered for treatment (3–7). For example, Cicero et al. (8) state that males might have a greater analgesic response to opiate medication than females, whereas Ciccone (7) suggests that men need a higher amount of medication for equivalent effects. However, few of these considerations enter medication guidelines in the procedure room (7,9). Because one might expect sex (the genetic aspect) and gender (the socialization component) to influence patients' experience and needs, we evaluated whether men and women differ in their drug-seeking behavior and their experience of anxiety and

Acad Radiol 2004; 11:390–397

[1] From the Harvard Medical School, Beth Israel Deaconess Medical Center, Interventional Radiology (V.J.S., E.V.L.), Boston, MA; Departments of Radiology and Psychology (K.S.B.) and Department of Psychology (S.L.), University of Iowa, Iowa City, IA; University of Florida, Public Health Services and Research (H.L.), Gainesville, FL; Health Research and Policy Centers, University of Illinois at Chicago (M.B.), Chicago, IL. 15 July 2003; accepted 11 October 2003. Supported by National Center for Complementary and Alternative Medicine RO1 AT 0002-06 and K24 AT 01074, National Institutes of Health. **Address correspondence to** Elvira V. Lang e-mail: elang@bidmc.harvard.edu

doi:10.1016/S1076-6332(03)00674-3

Table 1
Subject Characteristics

Characteristic	Standard Group (N = 79)		Attention Group (N = 80)	
	Men (n = 36)	Women (n = 43)	Men (n = 40)	Women (n = 40)
Age (yr); average (range)	54 (19–82)	56 (20–92)	58 (24–84)	51 (18–80)
Weight (kg); average	79.92	73.71	85.23	73.71
Race				
White	32	42	39	36
Black	4	1	1	4
Procedure				
Arterial	24	19	26	23
Venous	8	11	11	6
Arterial and venous	1	4	1	5
Nephrostomy	3	9	2	6
Disease Category*				
Category 1	9	15	14	20
Category 2	21	20	21	16
Category 3	5	7	5	3
Category 4	1	1	0	1
Prior procedures; average	5.12	4.15	6.23	4.35

*Disease categories: 1 = benign; no threat to limb or life; 2 = benign, threat to limb or organ, no threat to life; 3 = malignant, 4 = acutely life-threatening.

pain during interventional radiologic procedures. In addition, we introduced an empathic provider to evaluate the effect of social support on patient drug requests and pain and anxiety reports.

MATERIAL AND METHODS

Patients

Patient data were derived from the two control groups of a prospective randomized study of three groups that assessed the effect of a hypnotic intervention on patients' comfort during interventional radiologic procedures (10). In this study, 241 patients were randomized into a standard group (n = 79), attention group (n = 80), and hypnosis group (n = 82). The prior publication of this study did not assess the effects of sex and gender; this is a subsequent analysis of data.

Patients in the standard group received the standard of care typical for the institution; attending nurses were instructed to behave naturally and to do their best to comfort the patients. However, interaction with the patient during the procedure was inconsistent.

In the attention group of the original study, an additional provider stayed with the patients throughout the procedure and displayed a standardized empathic behavior. This group, originally designed to account for the effect of socialization that would inevitably take place in the hypnotic intervention group, lacked the therapeutic ingredient (hypnosis). The attention group, therefore, seemed ideally suited for the purpose of this new study. The original study's hypnosis group was omitted because it contained a treatment intervention that is not yet standard in a procedure suite.

Subjects for the study were patients referred for diagnostic and therapeutic peripheral arterial, venous, and percutaneous renal interventions, and who were able and willing to give written informed consent. Excluded were those who suffered from severe chronic obstructive pulmonary disease, psychosis, intolerance toward midazolam or fentanyl, those who were pregnant, unable to hear or understand English, or failed the Mini-Mental State Exam with a cutoff of 24 of 30 possible points (11).

The study comprised 159 patients: 79 patients under standard care and 80 patients in the attention group. Ages were 18 to 92 years (average 55 years); 76 of 159 (48%) were men (Table 1). Randomization resulted in relatively homogenous groups of patients; there were no significant differences between the two groups on key characteristics such as baseline pain and anxiety levels. No patients withdrew from the study during the time of observation.

Empathic Providers

The additional provider remained in close proximity to the patient during the entire procedure. Providers were two male and two female staff members (one female nurse, one male psychology graduate student, and two medical students). A training manual (published in abbreviated form [(12)] was used to define and standardize attentive behavior. Structured attentive behavior included matching verbal and nonverbal communication patterns (eg, sitting at the same height as the patient), attentive listening, giving the patient a feeling of control over the situation ("Let us know at any time what we can do for you"), encouragement, and avoidance of negatively loaded suggestions (eg, "How bad is your pain?" or "You will feel a sting and burn now"). Patients were instructed to concentrate on a competing feeling such as fullness, numbness, coolness, or warmth when painful stimuli were imminent.

Assessment of Pain and Anxiety

Patients were asked before and every 15 minutes during the procedure to rate their pain and anxiety on 0–10 linear numerical scales. Because dimmed lights and immobilization of patients in the X-ray equipment made the use of visual scales cumbersome, verbal scales were used with 0 = no pain at all and 10 = worst pain imaginable, and 0 = no anxiety at all and 10 = terrified. Such verbal pain scales have been validated for clinical research (13,14). Reliability and validity of the verbally administered anxiety rating has been shown previously (15).

Drugs

Drugs were administered in a patient-controlled analgesia/sedation model that would reflect patients' needs and drug-seeking behavior. Patient-controlled analgesia/sedation is well suited for acute pain management during and after medical procedures and is thought to enhance comfort while providing patients with a means of control (16,17). Patients were given a button that signaled the attending nurse to deliver, through an indwelling intravenous access, 0.5 mg of midazolam + 25 μg of fentanyl per request up to four times, with a lockout time of 5 minutes, with a subsequent lockout time of 15 minutes. Medication was withheld during the lockout times or if systolic blood pressure was $<$ 89 mm Hg, oxygen saturation fell below 89%, or the patient developed slurred speech or became poorly arousable. Fentanyl and midazolam, in addition to patient-controlled analgesia/sedation, were given for safety when patients spontaneously complained of significant distress, moved excessively so that the procedure was jeopardized, verbally requested medication, or blood pressure rose de novo above 180 mm Hg and did not normalize after 20 mg of nifedipine. This dosage regimen is within the standard of care for interventional procedures and is customary at the institution. Drug use was calculated in drug units by designating that 1 mg of midazolam = 1 unit and 50 μg of fentanyl = 1 unit.

Statistical Methods

Effects of treatment on total units of drugs requested and administered and on total procedure duration were studied among the 159 patients using univariate analysis of variance with a between-patient factor for treatment group (standard, attention) and another between-patient factor for sex group. Before analysis, logarithmic transformations were applied to remove skewness from the data (ln (x + 1), or ln (x) if x could not be 0); however, all results were presented in terms of the original scales (18). These latter two analyses were repeated using patient weight and age as covariates to assess their impact as an explanation of differences in drug use between the sexes.

The repeated measured analysis of pain responses was designed to characterize and compare trends in patients' pain ratings for the two treatment conditions crossed with sex groups (76 male patients, 83 female patients) over time (19,20), because previous studies have shown that pain increases over time. The analysis employed reports from as many as 13 successive 15-minute intervals. The dependent variable for these analyses was ln (pain score + 1) to correct skewness; residuals appeared normally distributed, and no outliers were identified. For descriptive flexibility, the statistical models included separate parameters for intercepts and linear trends. Correlations among residuals differed according to the time between observations, declining with increasing separation (termed a banded or Toeplitz covariance structure), and reaching negligible levels after six intervals; there was a slight decrease in error variability in later intervals, but not enough to model. These linear mixed models were estimated using restricted maximum likelihood in BioMeDical Program (BMDP) program 5V (21), which provides unbiased estimates of the intercepts and slopes; comparisons among slopes employed two-tailed Wald statistics. Similar analyses were conducted for anxiety.

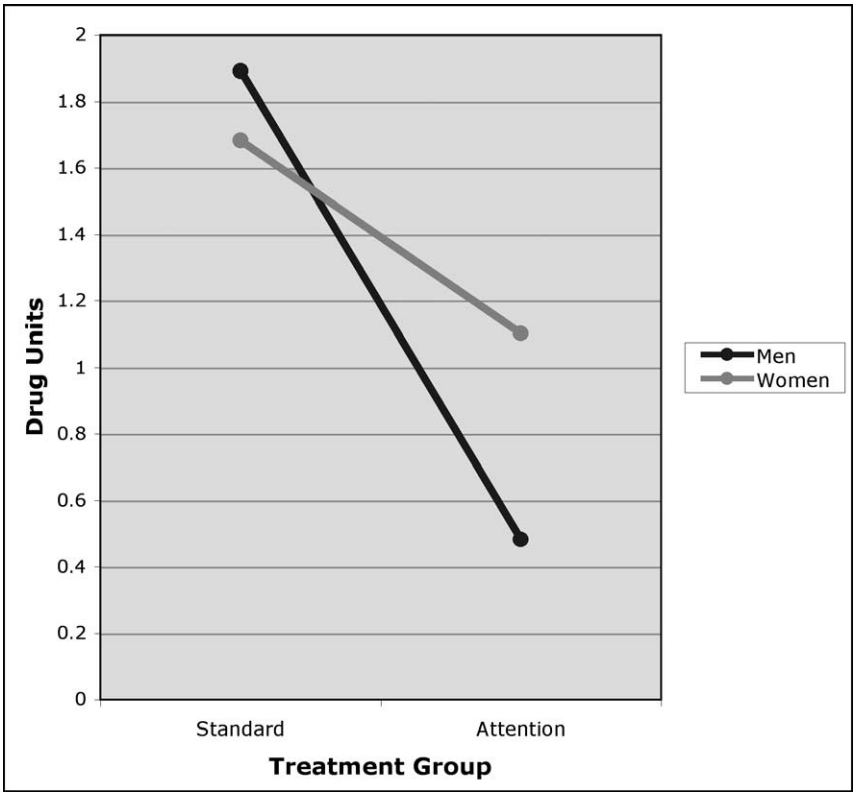

Figure 1. Drug request by men and women in the standard and attention group.

RESULTS

Procedure Duration and Medication Use

Patients rarely received drugs beyond their requests; if they did, they were given small amounts that did not affect the overall outcome. Results are therefore given in terms of drugs requested, not total drugs received. A two-way analysis of variance demonstrated a significant main effect of treatment group (standard group = 1.9 drug units requested, attention group = 0.8 drug units requested, F [1,155] = 20.47, $P < .0001$). The main effect of sex was not statistically significant, but the interaction of treatment by sex was statistically significant (F [1,155] = 4.63, $P < .05$) such that the difference between medication requested in the standard group and attention group was greater for males (1.4 drug units) than for females (0.6 drug units) (Fig. 1). The same differences remained when these analyses were repeated using weight and age as covariates.

Time Course of Pain

The intercepts for all four treatment-by-sex combinations were significantly different from zero ($P < .0001$), but not significantly different from each other: patients reported mild pain from the beginning of the procedure with no difference in amount between the sexes or treatments (Fig. 2).

Male patients.—Pain increased significantly over time in the standard group (slope = .07, $P < .01$), and had an upward trend in the attention group (slope = .06, $P = .089$). The difference in the pain trends between the two groups was not significant ($P = .78$).

Female patients.—Pain increased significantly over time in the standard group (slope = 0.11, $P < .0001$), but not in the attention group (slope = .03, $P = .33$). The difference in the pain trends between the two groups was significant ($P < 0.05$). This resulted in a widening gap between the curves for standard and attention patients as the procedures continued over time, which can be seen in Fig. 2. Note that this was not the case for men.

Time Course of Anxiety

The intercepts for all four treatment-by-sex combinations were significantly different from zero ($P < 0.0001$), but not significantly different from each other; patients were anxious from the beginning of the procedure with

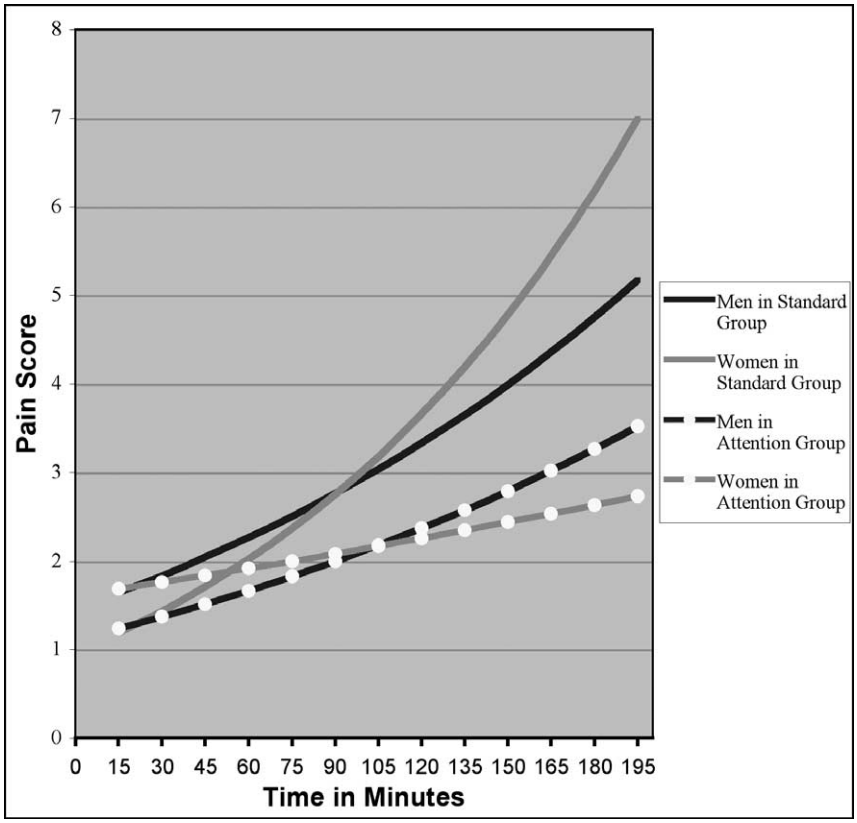

Figure 2. Reported pain by men and women over time in standard and attention group.

no difference in amount between the sexes or treatments (Fig. 3).

Male patients.—There was a significant linear trend downward in anxiety for men in the standard group (slope = −0.06, $P < 0.001$) and the attention group (slope = −0.08, $P < 0.05$). The difference in anxiety trends over time between the two groups was not significant ($P = 0.60$).

Female patients.—A significant linear downward trend in anxiety was seen in the attention group only (slope = −0.06, $p < 0.001$), but not in the standard group (slope = −0.02, $P = 0.161$). This difference in anxiety trends over time was significant between the two groups ($P < .05$). These results in a widening gap between the curves for standard and attention patients as the procedures continued over time, which can be seen in Fig. 3. Note again that this was not the case for men.

Significant effects of sex.—The difference in slopes between men and women was significant in the standard group ($P < .05$), but not in the attention group ($P = .56$).

DISCUSSION

In this study, both men and women requested significantly fewer drugs in the presence of an additional empathic provider, but the effect was much more pronounced for men. A significant difference in drug-seeking behavior between men and women only appeared when the interaction between treatment (presence or absence of the provider) and sex was tested. This strong dependence on the treatment setting, in which drugs are taken for the management of acute pain, may explain the varying results in the literature regarding gender differences. Men, for example, have been shown to request more drugs than women after surgery when given access to patient-controlled analgesia (22,23), a setting closest to our standard group condition. Terruzzi et al. (24), on the other hand, found a different gender effect. They conducted a study in which 249 patients undergoing colonoscopy were randomized to receive a fixed amount of intravenous midazolam (0.07 mg/kg) and meperidine (0.77 mg/kg) either immediately before colonoscopy or "on demand" during

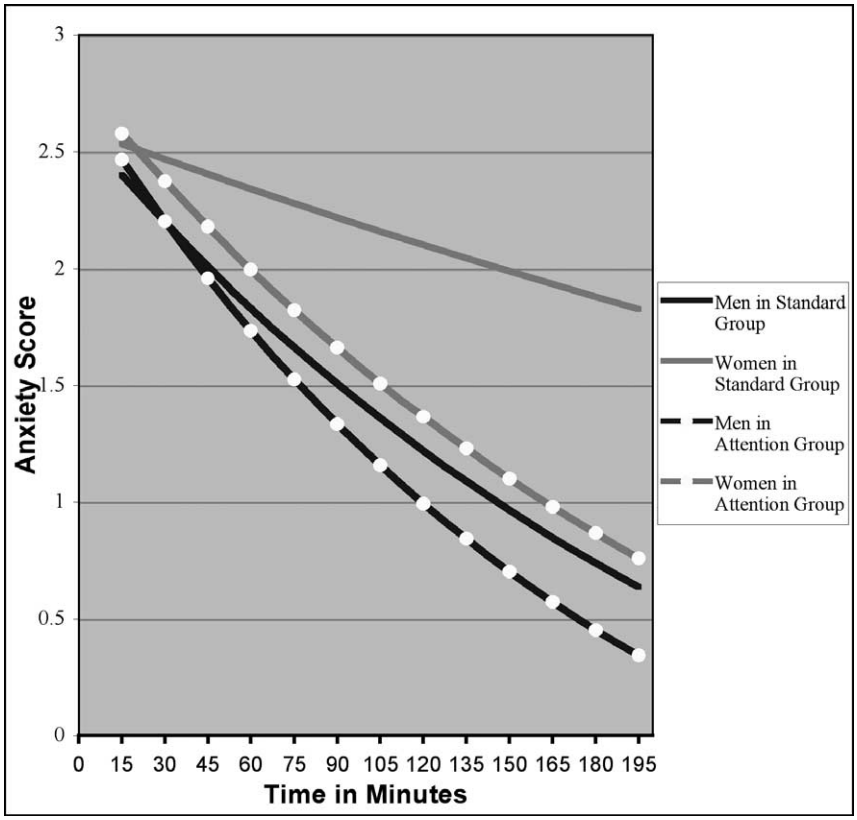

Figure 3. Reported anxiety by men and women over time in standard and attention group.

colonoscopy. In this study, male gender was associated with a lesser probability of drug requests in the "on demand" group when compared with women. This medication approach using only one fixed dose, however, is not a true patient-controlled analgesia/sedation model, and may also explain why 22% of all patients in the "on demand" group would not be willing to undergo colonoscopy in the future. One could speculate that this approach provided insufficient analgesia.

Conceptual considerations can explain both men and women needing more drugs: Cicero (8) states that men might have a greater analgesic response to opiate medication than females, and would be expected to need fewer drugs. On the other hand, Ciccone (7) concludes that women need fewer drugs because, on average, they have a lower body mass and thus fewer adrenergic receptors. But women also have a greater relative volume of distribution for highly lipophilic drugs than men (1.28 L/kg as compared with 1.0 L/kg). In our study, results still held after corrections were made for weight and age. This further highlights the need to observe the context in which drugs were sought.

Although men benefited more than women from the additional provider in terms of reduced drug use, they benefited less than women in terms of pain and anxiety relief. The difference in the reporting of pain and anxiety between the sexes seemed to be driven predominantly by the relatively poor experience of women under standard care conditions (Figs. 2 and 3).

In our study, men and women in both treatment groups reported similar pain levels at the beginning of the procedure and showed relatively similar and flat curves of pain ratings over time in the attention group (men had a marginal increase in pain over time). Under standard conditions, men's pain increased significantly over time, but at a slope that was not significantly different from the slope in the attention group. For women, however, the increase in pain over time and the difference between attention and control conditions was highly significant, accounting for the increasing gap between the curves in Fig. 2.

The increase in pain over time in the standard group is consistent with laboratory research indicating that exposure to acute pain makes individuals more attentive to external cues, such that they report increasing pain over

time even in the absence of a painful stimulus (25). Previous pain research suggests sex-dependent differences in the response to noxious stimuli, with females displaying greater sensitivity (6). Thus a greater increase in pain over time would not be surprising. The findings under standard conditions also agree with population-based pain research (reviewed in (2), which has shown that women are more likely than men to report a variety of temporary and persistent pains; and to report more severe pain, more frequent pain, and longer duration of pain than men (6). Women are described more often as active copers when confronted with pain (44% of women versus 16% of men in a study of patients with chronic lower back pain) (2,26). Using drug requests as an external observable mechanism of coping, one can conclude that women's ability to cope is not superior to that of men under standard conditions. The situation, however, changes dramatically for women in the presence of an additional provider; their pain curves much more resemble the flatter trends found in men. However, this improvement in pain rating was not associated with the same reduction in drug use as found in men, suggesting that women adapted their drug requests to a level conducive to their comfort in this treatment setting.

When viewing the time curves for anxiety (Fig. 3), the relatively poor performance of women under standard conditions is even more striking. Anxiety ratings, as with pain ratings, started at comparable baseline values for men and women in both groups, and decreased similarly for men in the attention and standard groups and women in the attention group. Anxiety remained high for women in the standard group.

Previous studies have shown an interaction between pain and anxiety (1), but the mode of interaction is not clear, and is likely different among men and women (1). Sex differences in the organization of the nervous system and hormonal differences can modify the experience of anxiety and pain (2,5,7). The reduction in anxiety, and thus stress, may possibly be the additional provider's greatest contribution to women's comfort.

This study demonstrated that an additional provider who displays structured empathic behavior has powerful beneficial effects on comfort and drug use during interventional radiologic procedures. Whether the mere presence of an additional person would suffice or whether the behaviors displayed were "therapeutic" cannot be answered. Previous studies (27,28) have shown that social support is effective in attenuating particular indices of physiologic reactivity (ie, heart rate and salivary cortisol) and thus in reducing stress. The assumption is that empathy is helpful to patients. However, very few articles define empathy and how it can be measured reliably. Therefore, we took recourse to define the provider's behavior so that others can train and evaluate their personnel accordingly. Furthermore, an additional provider in the procedure room can be a source of distraction for the patients. Distraction has been shown to decrease pain in prior studies (29).

An interfering factor in our study could be the sex of the provider. It may be possible that patients rate their pain and anxiety differently in the presence of a provider of the opposite sex than they would if asked by a provider of the same sex (30). This study unfortunately did not permit a further differentiation, because only 17 patients in the standard group and 21 patients in the attention group had a male provider, which did not allow a meaningful statistical evaluation. Because there is a dominance of women in the nursing profession, we believe that our study reflects typical clinical settings.

One may argue that one provider may have been more "empathic" than another. However, analysis of the data in the original study from which these data derived did not demonstrate a provider effect. This is probably because all providers practiced the key components of structured attentive behavior based on a standardized and operationalized treatment manual (12). The display of similar empathic behavior by all providers during the procedures was also controlled by the recording of videotapes, which were randomly rated by independent research assistants.

Based on the findings of this study, we conclude that patients of both genders benefit from the presence of an empathic person during invasive medical procedures, although there are significant differences between men and women. Men benefit more in terms of medication reduction, whereas women benefit more in terms of pain and anxiety reduction. Awareness of these gender-specific effects can aid in formulation of patient-specific treatment plans. Standard dosage regimens should be replaced by a tailored dose of drugs for each individual patient, especially taking into consideration sex and gender differences, to provide optimal drug therapy.

REFERENCES

1. Jones A, Zachariae R. Gender, anxiety, and experimental pain sensitivity: an overview. J Am Med Womens Assoc 2002; 57:91–94.
2. Unruh A. Gender variations in clinical pain experience. Pain 1996; 65: 123–167.

3. Maixner W, Fillingim R, Booker D, Sigurdsson A, et al. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain. Pain 1995; 63:341–351.
4. Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD, et al. Kappa-opioids produce significantly greater analgesia in women than in men. Nat Med 1996; 2:1248–1250.
5. Sun L. Gender differences in pain sensitivity and responses to analgesia. J Gender-specific Med 1998; 1:28–30.
6. Riley JR, Wise EA, Myers CD, et al. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. Pain 1998; 74:181–187.
7. Ciccone GK, Holdcroft A. Drugs and sex differences: a review of drugs relating to anaesthesia. Br J Anaesth 1999; 82:255–265.
8. Cicero T, Nock B, Meyer E. Gender-related differences in the anti-nociceptive properties of morphine. J Pharmacol Exp Ther 1996; 279: 767–773.
9. Lang EV, Chen F, Fick LJ, Berbaum KS, et al. Determinants of intravenous conscious sedation for arteriography. JVIR 1998; 9:407–412.
10. Lang EV, Benotsch EG, Fick LJ, Lutgendorf S, Berbaum ML, Berbaum KS, et al. Adjunctive non-pharmacological analgesia for invasive medical procedures: a randomised trial. Lancet 2000; 355:1486–1490.
11. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": A practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res 1975; 12:189–198.
12. Lang EV, et al. Nonpharmacologic analgesia and anxiolysis for interventional radiological procedures. Semin Interventional Radiol 1999; 16:113–123.
13. Paice JA, Cohen FL. Validity of a verbally administered numeric rating scale to measure cancer pain intensity. Cancer Nurs 1997; 20:88–93.
14. Murphy D, McDonald A, Power A, et al. Measurement of pain: a comparison of the visual analogue with a nonvisual analogue scale. J Clin Pain 1988; 3:197–199.
15. Benotsch EG, Lang EV, Lutgendorf SK, et al. Rapid anxiety assessment in medical patients. Ann Behav Med 1998; 20:138, 199–203.
16. Duggleby W, Lander J. Patient-controlled analgesia for older adults. Clin Nurs Res 1992; 1:107–113.
17. Schelling G, Weber W, Mendl G, et al. Patient controlled analgesia for shock wave lithotripsy: the effect of self-administered alfentanil on pain intensity and drug requirement. J Urol 1996; 155:43–47.
18. Kirk RE. Experimental design, procedures for the behavioral sciences. 3rd ed. Pacific Grove, CA. p. 72–112, 144–154, 164–208: Brooks/Cole Publishing Company, 1995.
19. Jennrich RI, Schluchter MD. Unbalanced repeated-measures models with structured covariance matrices. Biometrics 1986; 42:805–820.
20. Laird NM, Ware JH. Random effects models for longitudinal data. Biometrics 1982; 38:963–974.
21. Dixon WJ. BMDP statistical software manual, volume 2 (to accompany release 7). Berkeley, CA. p. 1311–1352: University of California Press, 1992.
22. Macintyre P, Jarvis D. Age is the best provider of postoperative morphine requirements. Pain 1995; 64:357–364.
23. Burns J, Hodsman NBA, McLintock TTC, Gillies GWA, Kenny GNC, McArdle CS, et al. The influence of patient characteristics on the requirements for postoperative analgesia. Anaesthesia 1989; 44: 2–6.
24. Terruzzi VM, Radaelli F, Terreni N, et al. Routine versus "on demand" sedation and analgesia for colonoscopy: a prospective randomized controlled trail. Gastrointest Endosc 2001; 54:169–174.
25. Bayer TL, Coverdale JH, Chiang E, Bangs M, et al. The role of prior pain experience and expectancy in psychologically and physically induced pain. Pain 1998; 74:327–331.
26. Keogh EH. Gender, coping and the perception of pain. Pain 2002; 97: 195–201.
27. Thorsteinsson EB, James JE, Gregg ME. Effects of video-relayed social support on hemodynamic reactivity and salivary cortisol during laboratory-based behavioral challenge. Health Psychology 1998; 17: 436–444.
28. Thorsteinsson EB, James JE. A meta-analysis of the effects of experimental manipulations of social support during laboratory stress. Psychol Health 1999; 14:869–886.
29. Freeman R, Barabasz A, Barabasz M, et al. Hypnosis and distraction differ in their effect on cold pressor pain. Am J Clin Hypn 2000; 43: 137–148.
30. Levine FM, De Simone LL. The effects of experimenter gender on pain report in male and female subjects. Pain 1991; 44:69–72.