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Complementary Therapies for Gynecological and Other Surgery

By Judith J. Petry, MD

CURRENT SURGICAL PRACTICE ADDRESSES PRIMARILY TECHNICAL concerns; the psychological aspects of the surgical experience rarely are addressed. This article reviews the current literature on the effectiveness of relaxation techniques, hypnosis and suggestion, and imagery on modifying surgical outcomes.

Effects of Anxiety and Depression

A high level of anxiety accompanies the need for surgery, and depression is common among surgical patients. Both anxiety and depression are risk factors for surgical complications.

The effect of preoperative anxiety was demonstrated in a study of 24 male patients scheduled for inguinal hernia repair in a Veteran's Administration hospital. Higher psychosocial stress correlated with lower immune function both preoperatively and postoperatively as well as with poorer surgical outcome.[1] Compared to patients with low stress levels, patients with higher stress levels had significantly more postoperative complications ($P < 0.05$) and used three times more postoperative narcotics ($P < 0.05$). Those with lower preoperative immune function had the longest hospital stays ($P < 0.01$). These changes appeared to be related to the stress of surgery; at 30 days postoperative, immune function was comparable between high and low stress patients.

Even minor outpatient surgical procedures may increase anxiety levels and affect immune function. A series of 50 consecutive patients undergoing excision of pigmented nevi under local anesthesia were found to have a significant increase in preoperative anxiety (increased blood pressure, pulse rate, respiratory rate, and pain), as well as a significant change in CD56+ lymphocytes.[2] Women were significantly more anxious than men ($P < 0.01$) in this study.

Preoperative anxiety increased anesthetic requirements in a prospective cross-sectional study of 57 women undergoing laparoscopic tubal ligation under general anesthesia. Patients were divided

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into low, medium, and high anxiety groups (using the State-Trait Anxiety Inventory). High trait anxiety patients required significantly more propofol (an intravenous anesthetic) than the low trait anxiety group for induction and maintenance of anesthesia ($P = 0.01$ and 0.03). No correlation was found for state anxiety or coping style.[3]

A prospective study in 171 cardiac surgery patients found that patients preoperatively identified as "distressed" by a set of questionnaires and the Nottingham Health profile experienced significantly more cardiac events at one-year follow-up (16%) than non-distressed subjects (5%, $P < 0.02$).[4]

Preoperative depression may correlate negatively with surgical outcome. Two years after 158 patients underwent coronary artery bypass surgery, three (15.2%) of the 24 patients preoperatively classified as depressed had died compared to three deaths (2.2%) among 134 non-depressed patients (odds ratio 6.24; 95% confidence interval 1.18-32.98; $P = 0.046$).[5] One death in each group was cardiac-related; none of the deaths were by suicide or accident. Another prospective study of 102 lumbar surgery patients found that anxiety and depression, but not hostility, were correlated with poor outcome.[6]

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Personality Factors

A patient's psychological makeup (rarely taken into account in studies of psychological interventions) also may be an independent predictor of preoperative and postoperative anxiety and depression, as well as surgical outcome. A prospective pilot study of 23 cardiac surgery patients found that those with an internal locus of control (determined by the Multidimensional Health Locus of Control) used 40% less morphine (average 19.85 mg/d) by patient-controlled analgesia than those with an external locus of control (average 33.53 mg/d).[7] Of 20 patients awaiting heart transplantation, external locus of control correlated with preoperative anxiety and depression; external locus of control also correlated with postoperative anxiety and depression.[8]

One review of presurgical psychological interventions concluded that it is important to adjust information to the patients' personality traits (specifically locus of control and coping style), and that behavioral interventions were most effective when matched with patients coping styles and level of anxiety.[9] For example, a study of 40 patients found that a brief formal preoperative visit from an anesthetist increased anxiety in low-anxiety patients, but decreased anxiety in high-anxiety patients.[10] Integrating such individualized care into standard medical settings would be complex.

Relaxation Techniques

Several techniques have been employed to decrease anxiety in surgical patients. A randomized, double-blind study of 97 surgical patients reported in 1964 (patients were not even informed that they were in a research study, an ethical violation) compared 51 controls, who received a routine preoperative anesthesia visit the night before surgery with no discussion of postoperative pain, with 46 "Special Care" patients, who also received detailed information about postoperative pain in careful detail including what to expect, treatment, and how to use simple relaxation techniques to reduce pain.[11] They were visited again after the surgery and once or twice a day until discharge. The "Special Care" group used 50% less narcotics postoperatively and were deemed ready for discharge 2.7 days earlier than the control group. It is not clear whether the instructions on managing postoperative pain or the individualized daily attention (a combination of psychological methods, relaxation, and human caring contact) affected outcome. Subsequent to this study, the importance of an individualized approach in utilizing psychological preparation for surgery has been underscored by many investigators.

A randomized study of 30 women scheduled for hysterectomy compared desensitization and relaxation

training (n = 10) to attention control (a friendly visit) (n = 10) and untreated control groups (n = 10).[12] Relaxation training significantly decreased discomfort and reduced hospital stay (5.5 days in the control group, 4.7 days in the visitor group, and 4.2 days in the relaxation group). No significant differences in state and trait anxiety were found between the groups in this small study.

A randomized controlled study in 40 patients undergoing minor colorectal or anal surgery assigned 21 patients to receive preoperative relaxation instructions. Compared to levels taken immediately before induction of anesthesia, the relaxation group experienced increased post-surgical cortisol and adrenaline levels; in the 19 controls, levels were unaffected or tended to decline.[13] Despite this increased endocrine response, relaxation was associated with a significant reduction in state anxiety on the preoperative and first postoperative days, decreased maximal perioperative systolic and diastolic blood pressures (111.5/67.0 mm compared to 120.5/72.1 mm, $P < 0.001$ systolic, $P < 0.05$ diastolic), and decreased analgesic use over the two postoperative days (1.1 tablets compared to 2.8, $P < 0.05$). These apparently paradoxical effects invite more research.

Current research on preoperative relaxation techniques is complex and the best techniques have not been identified conclusively. Behavioral methods, especially if they are individualized, probably are helpful in most patients.

Hypnosis and Suggestion

Hypnosis, defined as "a state of attentive and focused concentration in which ... people are highly responsive to suggestion" has been extensively studied since the early 19th century practice of mesmerism was in vogue.[14]

A 1991 review of the literature on suggestion, relaxation, and hypnosis in surgery found that the four best-designed randomized studies demonstrated a benefit for surgical patients.[15] In three studies, intraoperative suggestion resulted in shorter hospital stays (7.1 vs. 8.4 days, and 8.6 vs. 11.1 days) and fewer postoperative complications (fever, bowel problems) in experimental groups compared to controls. The fourth study has been mentioned previously.[11] Other randomized studies reviewed by the authors found significant improvement in postoperative emotional state with preoperative and intraoperative suggestions. One used suggestion and taped hypnotic induction in 40 cardiac surgery patients and demonstrated a similar significant reduction in postoperative anxiety as well as reduction in diastolic blood pressure and blood transfusions compared to controls. Only two of 18 studies reviewed found no benefit for hypnosis: one used self-hypnosis in cardiac surgery patients and the other used intraoperative suggestions.

More recently, mixed results of self-hypnosis in 32 cardiac surgery patients were reported in a small randomized surgeon-blinded study.[16] No difference was found in length of ICU stay, hospital stay, morbidity, or mortality between the group that practiced self-hypnosis preoperatively and postoperatively and controls. The study group had low postoperative adherence (65%). Although postoperative tension, depression, anger, and fatigue were lower in the study group, use of postoperative analgesia was higher than the control group.

A prospective, randomized, partially blinded study of 60 oral surgery patients tested daily use of a specially designed hypnotic audiotape for the week prior to surgery.[17] Patients in the audiotape group had a smaller mean increase in preoperative anxiety after using the audiotape (5.5 points) compared to the control group (11.7 points, $P = 0.03$). No difference was noted in pain medication use or complications. Analgesic use was similar between groups; unexpectedly, the experimental group had significantly more vomiting than controls (1.28 episodes compared to 0.27 episodes, $P = 0.006$). An audiotape may be inadequate for inducing hypnosis and is certainly inferior to a personal approach by a trained hypnotist. A serious flaw in this study was the lack of assessment of whether patients listening to the audiotape entered a hypnotic state.

More recently, a hypnosis study of 60 patients undergoing elective plastic surgery under conscious sedation randomized 35 subjects to hypnosis and 25 to an emotional support group.[18] The same anesthesiologist attended all patients; the intervention consisted of immediate preoperative and intraoperative induction of hypnotic trance; the emotional support group received instruction in stress reduction techniques with continuous verbal support, procedural information, reassurance and distraction, and pharmacological conscious sedation. Anxiolytic and analgesic drugs were administered as needed. Compared to the relaxation group, the hypnosis group had a significantly less need for pharmacologic sedation ($P < 0.001$), reduced intra- and postoperative pain scores ($P < 0.02$), less postoperative anxiety ($P < 0.04$), less postoperative nausea and vomiting (6.5% vs. 30.8%, $P < 0.001$), and increased perception of intraoperative control ($P < 0.01$). Patient satisfaction and comfort, surgeon satisfaction, and intraoperative stability of vital signs also were significantly better in the hypnosis group compared to the relaxation group. Limitations of the study were lack of blinding, use of the same anesthesiologist/hypnotherapist for both groups, and a short exposure to the relaxation technique.

Other recent studies have found favorable effects of hypnosis. A randomized controlled trial of 50 women

undergoing elective breast reduction surgery found that use of preoperative hypnosis and mental preparation (using an audiotape) resulted in significantly less vomiting (39% compared to 68% in the control group), less nausea (43.5% vs. 80%), and less need of postoperative analgesics.[19] No differences were found in pain, well-being, or degree of recovery over the first five postoperative days. A prospective clinical trial in 60 hand surgery patients compared preoperative hypnotic suggestion and relaxation to standard care; the treatment group showed significant decreases in pain (intensity and affect) and state anxiety, and fewer complications ($P = 0.004$). Surgeons who were blinded to group status rated hypnosis patients as making significantly better progress than controls ($P = 0.004$).[20]

Comparison of studies on hypnosis in surgery are difficult due to differences in types of hypnotic suggestion, patient expectations, hypnotic induction by audiotape vs. live therapist, and differences in hypnotizability of subjects (15-20% of the population is highly hypnotizable, 15-20% have low susceptibility to hypnosis, and the remainder of the population is in the mid-range). Ideally, patients should be tested for hypnotizability before resources are expended that will have little chance of success in specific individuals who can be identified beforehand. Overall, studies on the effects of hypnosis in surgery indicate that it is beneficial.

Imagery

Imagery has been defined as "both a mental process (as in imagining) and a wide variety of procedures used in therapy to encourage changes in attitude, behavior, or physiological reactions. It includes, as well as the visual, all the senses—aural, tactile, olfactory, proprioceptive, and kinesthetic."[21] Jeanne Achterberg, PhD, president of the Association for Transpersonal Psychology, has stated that imagery is "the communication mechanism between perception, emotion, and bodily change." In guided imagery, specific narratives are used in an attempt to focus and direct the imagination to enhance physical and emotional healing. Treatment imagery asks patients to imagine, for example, blood flow slowing at the surgical site during surgery to decrease blood loss. Healing or end-state imagery asks patients to imagine themselves the way they want to be. Imagery is a component of many practices, including biofeedback, neurolinguistic programming, autogenic training, and desensitization techniques; the discussion here of imagery focuses on studies that used imagery techniques.

A randomized controlled trial of 51 abdominal surgery patients compared controls (who received background information about the hospital preoperatively) to a group that received imagery training aimed not at anxiety reduction, but at increasing the patient's confidence to cope with surgical stress.[22] State anxiety was similar in both groups, but imagery patients experienced less postoperative pain ($P < 0.05$), were less distressed ($P < 0.01$), felt they coped with pain better ($P < 0.01$), and requested less pain medication ($P < 0.05$) than controls. Compared to controls, cortisol levels were lower and noradrenaline levels higher immediately preoperatively and postoperatively in imagery patients ($P < 0.01$).

A randomized study of 32 general surgery patients (90.5% female) gave all patients procedural information; 16 also underwent imagery training designed to relieve postoperative pain ($n = 16$).[23] Study subjects experienced significantly less postoperative pain ($P < 0.001$), measured by visual analog scale, and took fewer postoperative analgesics ($P < 0.03$) than controls.

The best study to date of imagery and surgical outcome is a randomized controlled trial that compared guided imagery to standard preoperative preparation in 130 patients undergoing elective colorectal surgical procedures.[24] Compared to controls, the 65 imagery patients experienced significantly less preoperative and postoperative anxiety ($P < 0.001$), less postoperative pain ($P < 0.001$), earlier first bowel movements ($P < 0.001$), and required almost 50% less postoperative narcotics ($P < 0.001$). Different researchers using a similar design and similar imagery technique reported a follow-up. A randomized controlled study of 86 patients undergoing anorectal surgery for benign disease, utilizing a similar imagery technique, found that imagery patients experienced better quality of sleep ($P = 0.01$) than control patients.[25]

Some types of imagery may have adverse effects; a study using hypnotic suggestion in cardiac surgery patients found that patients who used muscle relaxation imagery had significantly more chest tube drainage than those who used suggestion related to optimal surgical outcome and controls.[26]

Conclusion

In appropriately designed interventions, relaxation techniques, hypnosis and suggestion, and imagery are safe; techniques designed specifically to improve surgical outcomes deserve more attention and careful implementation in surgical settings. Mind/body techniques may be of significant benefit with regard to patient satisfaction, preoperative and postoperative anxiety and depression, anesthetic requirements, intraoperative vital signs, postoperative pain, nausea and vomiting, analgesic requirements, complications, and hospital

stay. Improvements in these outcomes would offer significant cost savings, as well as improved physical and emotional results. Cost-benefit studies for specific interventions are needed. ❖

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St. John's Wort and Depression

Source: Shelton RC, et al. Effectiveness of St. John's wort in major depression: A randomized controlled trial. *JAMA* 2001;285:1978-1986.

Design and Setting: Randomized, double-blind, placebo-controlled, multicenter clinical trial. Subjects underwent a one-week, single-blind placebo run-in; those whose HAM-D scores improved by 25% or fell to < 20 were excluded.

Subjects: Two hundred adult outpatients (67.0% female; 85.9% white) with major depression and Hamilton depression (HAM-D) 17-item scale scores of ≥ 20.

Treatment/Dose/Route/Duration: Placebo or a standardized extract of St. John's wort 300 mg (Lichtwer Pharma GmbH) tid for eight weeks; after four weeks, if no effect was seen, the dose was increased to four tablets daily (1,200 mg).

Outcome Measures: HAM-D scores analyzed by a random coefficient regression model that examined differences in linear rate of change. Secondary efficacy variables included the Beck depression inventory, Hamilton rating scale for anxiety (HAM-A) the global assessment of functions scale (GAF), the clinical global impression-severity (CGI-S) and -improvement (CGI-I) scales. An intention-to-treat (ITT) analysis was done; a secondary subgroup analysis included only patients with a baseline HAM-D score of ≥ 22. Differences in response and remission rates were examined using Cochran-Mantel-Haenszel tests. Assessments of safety and efficacy were made at the end of weeks 1, 2, 4, 6, and 8.

Results: There were no significant differences between groups in any of the assessment scales. There were significant effects for time but not for treatment or time by treatment interaction. The proportion of subjects who responded was not different between groups. The only significant treatment effect was the number of remissions, which was significantly higher in the treated group (14/98 [14.3%]) than in the placebo group (5/102 [4.9%]). The treatment was well-tolerated. However, 41% of those treated with St. John's wort experienced headache compared to 25% in the placebo group, a significant difference.

Funding: Pfizer Inc. (which manufactures both pharmaceutical antidepressants and St. John's wort extracts).

COMMENTS BY ADRIANE FUGH-BERMAN, MD AND STEVEN BRATMAN, MD

Although this was a well-designed trial, the write-up is deficient. The attention to design details is laudable: for example, care was taken to mask the taste and smell of the verum treatment; individual lots of the treatment were analyzed to ensure consistency; a dose increase was built in; and HAM-D assessments were videotaped and reviewed by an independent assessor. In addition, the study population appears to have been selected to represent an appropriate level of depression for comparison with previous St. John's wort studies: The median entry score of 22 on the 17-item HAM-D is very close to the entry scores seen in, for example, two recent trials, a three-armed trial comparing St. John's wort to imipramine and placebo in 263 participants,[1] and another comparing St. John's wort to imipramine in 324 participants.[2]

The presentation of results, however, raises questions about the heterogeneity of the study population. Given that there were 14 remissions in the St. John's wort group and five in the placebo group, responses must have been quite heterogeneous for the graph of HAM-D scores (presented as unadjusted means) to show the two groups almost overlapping. It would have been nice to see the actual distribution of scores. The mean "duration of current major depressive disorder" was 2.3 years (SD 6.3) in the St. John's wort group and 2.7 years (SD 5.6) in the placebo group. Assuming that this number refers to time elapsed since the diagnosis of major depressive disorder (if it refers to the duration of the current episode, these patients would be atypically chronic), the standard deviations show that the distribution is dramatically skewed. It raises the question of whether the outliers unbalance the population enough to affect results.

The investigators' designation of subjects with a Hamilton score of < 22 as less severely depressed is idiosyncratic. Within this trial, this could only include subjects with a HAM-D score of 20 or 21, and it is entirely arbitrary to designate someone with a score of 21 as less severely depressed than someone with a score of 22. The single positive finding in this trial was a higher remission rate among the treated group. Although remission rates were low, the authors should not have dismissed this finding; remission is of clearer benefit to the patient than an improvement in HAM-D scores.

The desire that one's research will supersede all other research in the field is probably common, but most authors are better at keeping such uncollegial thoughts under wraps. The table entitled "Design limitations of previous controlled trials of St. John's wort" purports to document deficiencies in design but actually contains mainly opinions, that although framed in table cells are still opinions.

The seven column titles are: Diagnostic practices/ heterogeneity; Less experienced investigators; No

standardized symptom ratings; Low depression severity; Small sample size/inadequate power; Low comparator dose/no plasma levels; and Low St. John's wort dose. Trials are assessed by single checkmarks in the columns. Of the seven criteria, the charge of diagnostic practices/heterogeneity is fair and the claim that this affects almost all previous trials is probably accurate. Lack of standardized symptom ratings is also a fair study limitation (but this only affects 7/31 trials).

The category of "Less experienced investigators" seems both vague and subjective; the only explanation given of how this was assessed is "use of investigators without apparent experience in psychiatry or research." This may refer to a major difference in subject recruitment; in the United States, it is common for a small number of investigators to recruit a relatively large number of patients, often through advertising. In Germany, most studies are performed by a relatively large number of primary care physicians, each recruiting a relatively small number of patients from within their practices. One system has not been proven better than the other.

The designation of "Low depression severity," defined as the inclusion of mildly depressed subjects with HAM-D scores of < 18, as a methodological flaw is peculiar (deliberate inclusion of mildly depressed subjects is hardly a design flaw). "Small sample size/inadequate power" is explained only by saying that "statistical power was too low to detect meaningful differences between groups." This is nonsensical in placebo-controlled trials (12/17 checked in this column); if differences were detected between groups, then power simply is not an issue. The statement could be defended for treatment-controlled trials, but even by the authors' unknown criteria, this only affects five of 14 treatment-controlled trials.

"Low comparator dose/no plasma levels" (affecting 13 studies) also is unfair, as well as an odd pairing (it is not indicated which charge applies to each study). Although the doses of (primarily tricyclic) drugs used as comparators in some studies are less than those routinely used as starting doses in the United States, the doses were standard therapeutic doses when and where the studies were performed. The majority of trials (including the largest and most recent) used adequate doses of antidepressants. Lack of antidepressant plasma levels should not be considered a methodological flaw when such levels are not routinely required in depression studies.

"Low St. John's wort dose" (defined as" < 600 mg/d standardized hypericin concentration)" is idiosyncratic. "Standardized hypericin concentration" is meaningless without an indication of the concentration (the usual standardized extract would provide 2.7 mg/d hypericin), but, that aside, lower doses of 350-500 mg/d St. John's wort extract (containing 0.5-0.75 mg/d hypericin) have achieved positive results against placebo in at least four placebo-controlled trials.[3] (Hypericin is only one of the potential active ingredients in St. John's wort). Although the 900 mg dose has become the standard, this is not based on data. The authors themselves are not wedded to 900 mg, as one of their exclusion criteria was a "prior adequate trial of St. John's wort (at least 450 mg/d)."

Study duration also is criticized in the text, despite the fact that the current eight-week study is not markedly longer than previous studies (20/31 were ≥ six weeks). Finally, one recent study was inexplicably omitted: A 42-day double-blind, placebo-controlled trial of 142 participants with mild-to-moderate depression according to DSM IV criteria.[4] ❖

Dr. Bratman is Medical Director and Senior Editor of TNP.com.

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In The News

Renal Toxins in *Aristolochia*

The FDA has released a letter warning health professionals to watch for interstitial fibrosis associated with end-stage renal disease (ESRD), or urothelial tract tumors, connected with use of aristolochic acid-containing dietary supplements. In Belgium, approximately 100 cases of renal disease were reported in patients who took weight-reducing pills containing *Aristolochia fangchi* between 1990-1992. Since then, two cases of interstitial fibrosis in the United Kingdom, seven cases in France, and two cases in the United States have been linked to botanical preparations containing aristolochic acid. In

2000, it was reported that among 39 patients with ESRD from the original Belgian cohort who underwent surgery, 18 cases (46%) of urothelial carcinoma were identified; all tissue samples contained aristolochic acid-related DNA adducts. Aristolochic acid has been identified in several botanical products sold in the United States. These include single-ingredient products labeled as *Aristolochia* (sometimes called Virginia snakeroot), botanicals likely to be substituted with Aristolochia (e.g., *Stephania tetrandra*, *Clematis armandii*, and *Akebia* extract), and several finished products sold as dietary supplements. Warning letters and recall requests have been issued. Cases of renal disease or malignancies associated with the use of botanical preparations should be reported as soon as possible to FDA's MedWatch program by telephone (1-800-332-1088) or Internet (http://www.fda.gov/medwatch). For additional information, see http://www.cfsan.fda.gov/~dms/ds-bot.html. ▼

'Digestive Aid' Recalled

Solgar Vitamin and Herb Company has recalled two lots of its Digestive Aid dietary supplements due to possible *Salmonella* contamination. The supplement contains pepsin, which routine sampling revealed was contaminated with *Salmonella*. Recalled lots are 31993 or 30957 (lot numbers are above the expiration date on the bottle neck).

No illnesses have been reported to date. For further information, see FDA Talk Paper "Solgar vitamin and herb company recalls Solgar's Digestive Aid 100's dietary supplements because of possible salmonella contamination." Available at: http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01081.html. ▼

Dangers of 1,4-butanediol

GHB (gamma hydroxybutyrate, an ergogenic agent and recreational central nervous system depressant drug popular in the 1980s) was linked to 71 deaths and has been banned for sale since 1990. However, 1,4-butanediol, a GHB precursor, still is available over the counter. Promoted as an ergogenic agent or for treating depression or insomnia, 1,4-butanediol is both toxic and habit-forming. Toxic effects include vomiting, urinary and fecal incontinence, agitation, combativeness, a labile level of consciousness, respiratory depression, and death. A review of nine recent cases of 1,4-butanediol intoxication found that two died (doses ranged from 1-14 g in nonfatal cases and from 5.4 -20 g in fatal cases). Gamma-butyrolactone (another GHB precursor) supplements were voluntarily recalled in 1999; in a one-year period ending April 1999, the FDA received 119 reports of toxic effects associated with gamma-butyrolactone, including two deaths.

1,4-butanediol usually is listed on labels as tetramethylene glycol, butylene glycol, or sucol-B; dietary supplements containing 1,4-butanediol include Rejuv@Nite, Ultradiol, Enliven, N-force, Liquid Gold, Zen, Soma Solutions, Blue Raine, Thunder, Serenity, NRG3, Thunder Nectar, InnerG, SomatoPro, Weight Belt Cleaner, X-12, Rest-Q, Biocopia PM, Dormir, and Amino Flex. Both 1,4-butanediol and gamma-butyrolactone (often listed as furanone, furanone dihydro, lactone, or GBL) are also found in "natural" cleaners and solvents. Gamma-hydroxybutyrate-related compounds will not show up on routine toxicology tests; targeted analysis with gas chromatography-mass spectrometry is needed. ❖

Source: Zvosec DL, et al. Adverse events, including death, associated with the use of 1,4-butanediol. *N Engl J Med* 2001;344:87-94.

CME Questions

24. Which of the following may be correlated with poor surgical outcome?
a. Anxiety
b. Depression
c. Both anxiety and depression

25. What percent of the general population is highly hypnotizable?
a. 5-10%
b. 15-20%
c. 50%
d. 90-100%

26. Aristolochic acid in the Chinese herb *Aristolochia fangchi* has been associated with:
a. end-stage renal disease.
b. urothelial carcinoma.
c. both end-stage renal disease and urothelial carcinoma.

27. Toxic effects of the ergogenic dietary supplement 1,4 butanediol include:
a. agitation and combativeness.
b. urinary and fecal incontinence.
c. death.
d. All of the above

In Future Issues:

Marital Stress and Cardiovascular Disease
Exercise and Osteoporosis in Women
Black Cohosh