TIGAN®
(trimethobenzamide HCl)

Indications: Tigan is indicated for the control of nausea and vomiting.
Contraindications: The injectable form of Tigan in children, the suppositories in premature or newborn infants, and use in patients with known hypersensitivity to trimethobenzamide are contraindicated. Since the suppositories contain benzocaine they should not be used in patients known to be sensitive to this or similar local anesthetics.
Warnings:

Caution should be exercised when administering Tigan to children for the treatment of vomiting. Antiemetics are not recommended for treatment of uncomplicated vomiting in children and their use should be limited to prolonged vomiting of known etiology. There are three principal reasons for caution:

1. There has been some suspicion that centrally acting antiemetics may contribute, in combination with viral illnesses (a possible cause of vomiting in children), to development of Reye's syndrome, a potentially fatal acute childhood encephalopathy with visceral fatty degeneration, especially involving the liver. Although there is no confirmation of this suspicion, caution is nevertheless recommended.
2. The extrapyramidal symptoms which can occur secondary to Tigan may be confused with the central nervous system signs of an undiagnosed primary disease responsible for the vomiting, e.g. Reye's syndrome or other encephalopathy.
3. It has been suspected that drugs with hepatotoxic potential, such as Tigan, may unfavorably alter the course of Reye's syndrome. Such drugs should therefore be avoided in children whose signs and symptoms (vomiting) could represent Reye's syndrome. It should also be noted that salicylates and acetaminophen are hepatotoxic at large doses. Although it is not known that at usual doses they would represent a hazard in patients with the underlying hepatic disorder of Reye's syndrome, these drugs, too, should be avoided in children whose signs and symptoms could represent Reye's syndrome, unless alternative methods of controlling fever are not successful.

Tigan may produce drowsiness. Patients should not operate motor vehicles or other dangerous machinery until their individual responses have been determined. Reye's syndrome has been associated with the use of Tigan and other drugs, including antiemetics, although their contribution, if any, to the cause and course of the disease hasn't been established. This syndrome is characterized by an abrupt onset shortly following a nonspecific febrile illness, with persistent, severe vomiting, lethargy, irrational behavior, progressive encephalopathy leading to coma, convulsions and death.
Usage In Pregnancy: Trimethobenzamide hydrochloride was studied in reproduction experiments in rats and rabbits and no teratogenicity was suggested. The only effects observed were an increased percentage of embryonic resorptions or stillborn pups in rats administered 20 mg and 100 mg/kg and increased resorptions in rabbits receiving 100 mg/kg. In each study these adverse effects were attributed to one or two dams. The relevance to humans is not known. Since there is no adequate experience in pregnant or lactating women who have received this drug, safety in pregnancy or in nursing mothers has not been established.
Precautions: During the course of acute febrile illness, encephalitides, gastroenteritis, dehydration and electrolyte imbalance, especially in children and the elderly or debilitated, CNS reactions such as opisthotonos, convulsions, coma and extrapyramidal symptoms have been reported with and without use of Tigan or other antiemetic agents. In such disorders caution should be exercised in administering Tigan, particularly to patients who have recently received other CNS-acting agents (phenothiazines, barbiturates, belladonna derivatives). It is recommended that severe emesis should not be treated with an antiemetic drug alone; where possible the cause of vomiting should be established. Primary emphasis should be directed toward the restoration of body fluids and electrolyte balance, the relief of fever and relief of the causative disease process. Overhydration should be avoided since it may result in cerebral edema.
The antiemetic effects of Tigan may render diagnosis more difficult in such conditions as appendicitis and obscure signs of toxicity due to overdosage of other drugs.
Adverse Reactions: There have been reports of hypersensitivity reactions and Parkinson-like symptoms. There have been instances of hypotension reported following parenteral administration to surgical patients. There have been reports of blood dyscrasias, blurring of vision, coma, convulsions, depression of mood, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, muscle cramps and opisthotonos. If these occur, the administration of the drug should be discontinued. Allergic-type skin reactions have been observed; therefore, the drug should be discontinued at the first sign of sensitization. While these symptoms will usually disappear spontaneously, symptomatic treatment may be indicated in some cases.
Note: The injectable form is intended for intramuscular administration only; it is not recommended for intravenous use.
How Supplied: CAPSULES* 100 mg, 250 mg, Inactive Ingredients: Lactose, Magnesium Stearate and Starch.
SUPPOSITORIES* 100 mg, 200 mg, contains 2% benzocaine in a base compounded with polysorbate 80, white beeswax and propylene glycol monostearate.
INJECTABLES*† Ampuls: 100 mg/ml (2 ml) 0.2% parabens (methyl and propyl) as preservatives, 1 mg sodium citrate and 0.4 mg citric acid as buffers and pH adjusted to approximately 5.0 with sodium hydroxide.
Thera-Ject® Disposable Syringes: 100 mg/ml (2 ml) contains 200 mg trimethobenzamide hydrochloride compounded with 0.45% phenol as preservative, 1 mg sodium citrate and 0.4 mg citric acid as buffers, 0.2 mg disodium edetate as stabilizer and pH adjusted to approximately 5.0 with sodium hydroxide.
Vials: 100 mg/ml (20 ml) 0.45% phenol as preservative, 0.5 mg sodium citrate and 0.2 mg citric acid as buffers and pH adjusted to approximately 5.0 with sodium hydroxide.
*TIGAN, in all dosage forms, is contraindicated in premature and newborn infants.
†TIGAN injectables are contraindicated in children.

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LETTERS TO THE EDITOR

The Journal welcomes Letters to the Editor. If found suitable, they will be published as space allows. Letters should be typed double-spaced, should not exceed 400 words, and are subject to abridgment and other editorial changes in accordance with Journal style.

FATIGUE IN PRIMARY CARE

To the Editor:

Since there appears to be a consensus among family physicians that more inquiry is needed to improve our understanding of common health problems, and that research networks represent valuable resources for this type of study, one hesitates to criticize the investigation of fatigue by Kirk et al,[1] which utilized a 28-practice primary care research network in New England. A careful look at their report, however, suggests some causes for concern.

Twelve months elapsed in this study between initial selection of subjects and the final assignment of physical or psychological cause. During this interval 54% (83/154) of the original population was lost. That interval telephone interviews each required about 1 hour of the subjects' time[2] may have contributed to this attrition. With 20/20 hindsight, it might have been better to assess the cause of fatigue 1 month into the project, by which time diagnostic studies should have been completed, with a provision that any subsequent changes of diagnosis would be analyzed separately.

Forty-eight percent of the patients in this study were judged to have fatigue of primarily psychological causes. Unfortunately, this assessment applies only to the minority of subjects who were still being followed at the end. Taking the numbers in the paper and the authors' statement that dropouts had more psychological problems than the completers, one can conclude that a behavioral cause was primary in 48% ([34 + 40]/154) to 76% ([34 + 83]/154) of the entry population. These numbers are of interest in light of the recent report of Manu et al[3] that the overwhelming majority of referred patients with persistent complaints of fatigue have psychiatric disorders.

The paper under discussion has largely eschewed the *post hoc ergo propter hoc* fallacy, the pitfall of assuming that the association of variables indicates cause and effect, but the group's previously published work relating to the same project[2] contains the assertion "fatigue has wide-ranging impact on the quality of an individual's life." This wording suggests that the fatigue comes first and everything else follows. It would have been wiser to say that a complaint of fatigue is often associated with impaired well-being without assuming that it is the causative agent. At our present level of understanding, fatigue should be considered a symptom, not a disease.

Some specific questions for Dr Kirk and his associates:

1. Noting that psychological distress was more salient in their dropouts than in those who completed the study, I would be interested in the authors' views as to whether a significant part of their dropout rate might be a consequence of sick role behavior.[4] People who use fatigue or other symptoms as psychological "crutches" may feel threatened by the close scrutiny inherent in research of this type, leading them to withdraw from it.

2. Table 5 of the paper indicates that in 37% (26/71) of subjects there was discordance between physician and patient assessment as to whether the fatigue was primarily physical or psychological in origin. This rate seems high, as caregiver and patient had presumably been in communication for 12 months at the time assessment was made. Do the authors have an opinion as to why the concordance was not better? Might bias against behavioral diagnoses exist both in some of their subjects and in a few of their physicians?[5]

3. The paper is silent regarding standards for biomedical diagnoses. Was there, for example, agreement as to how severe anemia had to be before it was accepted as a cause of fatigue? Did they employ a standard patient workup, and if so, what did it include?

The needs of our patients call for many more investigations that attempt to evaluate human feelings and behavior, even though such work is inherently imprecise and difficult to conduct. At the same time, it is important to address the obstacles encountered in such research and their implications openly, even at the cost of possibly discouraging important work, if the end result is to be valid and useful.

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2. Nelson E, Kirk J, McHugo G, et al: Chief complaint fatigue: A longitudinal study from the patient's perspective. Fam Pract Res J 1987; 6(4):175–188
3. Manu P, Lane TJ, Matthews DA: The frequency of chronic fatigue syndrome in patients with symptoms of persistent fatigue. Ann Intern Med 1988; 109:554–556
4. Demers RY, Altamore R, Mustin H, et al: An exploration of the dimensions of illness behavior. J Fam Pract 1980; 11:1085–1092
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The preceding letter was referred to Dr Kirk, who responds as follows:

We appreciate Dr Gillette's kind words about the Dartmouth COOP Project. Indeed, we are proud of the contributions to primary care research our network of practitioners have made. We also share Dr Gillette's concern, however, that primary care research must be carried out in proper methodologic fashion and be able to stand up to careful scrutiny. His observations regarding our fatigue study provide some valuable insight into the limits and problems of office-based research.

We lost 46% of the original cohort (not 54%). Previous COOP studies had achieved much better response rates so that we were surprised and disappointed by the large attrition rate. It depended on the study relationship our practitioners have with their patients and a large investment in personnel to track the patients. The heavy response burden of the questionnaires and interviews, however, exceeded the tolerance of even this usually devoted group of patients. The common wisdom is borne out: Hospitalized patients will tolerate almost anything; ambulatory patients remain "in control" and have real limits. We would add that a significant number of our dropouts (27 of 71) did not refuse, but could not be reached for follow-up. Our interviewers reported that many of these were people who wintered in the South and for whom the practices had no forwarding address. We carefully chose the 1-year follow-up period knowing that such a long time might create problems. We were convinced, however, that we could get more accurate diagnostic impressions over a longer time, especially when we did not intend to intrude into the care process by having a fixed battery of tests done at the outset.

The dropout problem obviously has implications for the physical vs psychological classification. I am not sure of the origin of Dr Gillette's projections; but if we assumed, at worst, that all of the 71 dropouts would have been judged by the physicians to have primary psychologic causes of fatigue, the percentage of such origins would increase from the 37% we reported to 68% (26 and 71 dropouts/142). It seems that presumption would be extreme, though. The dropouts did show more evidence of psychologic illness on the entry questionnaire, but surely it cannot be assumed that the fatigue of all of these patients would have been classified by their physicians as having a psychologic origin. We wish we had achieved better follow-up to better answer this question, but our impression was that a surprisingly large number of our patients had physical conditions contributing to their fatigue in a primary or secondary way. We are uncertain as to the impact of sick role behavior on the dropout rate. In fact, we might state a contradictory hypothesis to that of Dr Gillette: that the more psychologically impaired might enjoy the scrutiny and interest of our researchers, resulting in a higher retention rate of such patients. We just do not know.

Dr Gillette rightfully takes issue with our wording "Fatigue has wide-ranging impact on the quality of an individual life." A causal relationship should not be assumed. We suspect that a circular relationship often exists between fatigue and other measures of impaired well-being.

Regarding the rate of agreement between physicians and patients as to cause of fatigue, one might consider the glass half-full or half-empty, depending on one's point of view. The reported concordance rate of 63% is even greater if "secondary" causes are also counted as in agreement. The frequency of secondary causes from the "other" category (41% of cases were judged by physicians to have causes both physical and psychologic) makes it harder to judge the agreement issue or to hypothesize about the physician-patient communication on the subject. It still seems that the physicians were more often giving the patients the benefit of the doubt by ascribing physical causes.

We did not attempt to standardize our diagnostic criteria. We did not feel that such attempts would bring us closer to the diagnostic "truth" with a (presumed) multifactorial symptom like fatigue. For example, how much congestive heart failure or emphysema or depression is needed to cause, or contribute to the cause of, fatigue? We felt that the most accurate appraisal would be provided by the patients' primary care physicians who had the benefit of 1 year of follow-up from the date of entry.

John Kirk, MD
The Dartmouth COOP Project
Hanover, New Hampshire

SLEEP LOSS AND COGNITIVE PERFORMANCE

To the Editor:

The article by Jacques et al on the effects of sleep loss on cognitive performance of residents (*Jacques CHM, Lynch JC, Samkoff JS: The effects of sleep loss on cognitive performance of resident physicians. J Fam Pract 1990; 30:223–229*) did not consider another possibility to explain their data: that less-prepared test takers might, consciously or unconsciously, self-report less sleep as an excuse for anticipated poor performance (even though the forms were coded), or that they stayed up reviewing the night before.

The large numbers of opposing data cited from other studies (showing both deterioration and no deterioration following loss of one night's sleep using the same tests) might indicate that no convincing answer will be forthcoming, no matter how many more times the effects of sleep loss are studied in large groups. Either sleep makes no difference in performance, or there are subsets within each large group, or even within each individual, that cancel each other out. This possibility is consistent with the common sense of the matter: we can all remember when, as residents, some nights of sleep deprivation seemed to affect our performance adversely while others seemed to render us even more "sharp" the next day, having gotten a "second wind." I wonder whether the authors have considered correlating serum cortisol, catecholamines, caffeine intake, etc.

Discrepant data will give all players the choice of which to use when arguing for and against changes in residency conditions.

Out here in the world, we may have to face an office full of patients after being up most of the night. There needs to be some preparation for that. Limiting on-call hours will not keep young people from other sleep-depriving activities. Though "mechanisms" are important, the practice of medicine is a cumulative accretion of knowledge and hands-on repetition. It takes a lot of hours in the hospital or clinic to see all you need to see.

Pepi Granat, MD
South Miami, Florida

The preceding letter was referred to Dr Jacques, who responds as follows:

There is no question that residency training must be rigorous and that the practice of medicine requires caring for patients at all hours of the day and night. I also agree with Dr Granat that preparation during the training program is necessary to prepare physicians for the difficulties of real-world medicine.

There is, however, a growing body of literature that strongly suggests that the loss of sleep encountered with traditional residency call schedules adversely affects both mood and performance. The article on sleep loss was not designed to suggest that training be compromised. Rather, what is needed is to look at the problem openly and objectively, change work schedules that place patients and residents at risk, and develop programs that best train physicians to recognize and deal with the problems imposed by sleep loss, fatigue, and other stresses of our profession:

Traditional methods of training physicians have produced outstanding physicians. Some aspects of the training process, however may have shaped attitudes and behaviors detrimental to the best interests of patients and physicians alike. It is time that we examine residency training closely. Perhaps the long hours it takes "to see all you need to see" can be distributed in a better way.

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USE OF SALT SUBSTITUTES

To the Editor:

Since the publication of "Salt Substitutes as a Source of Potassium" in *JAMA* in 1977,[1] I have routinely offered salt substitutes as an option to patients for whom I am initiating potassium supplementation and to new patients who are already taking potassium supplementation (who are universally on prescription products). My experience corresponds with the findings of Hueston,[2] but an important issue was not surfaced.

My experience with patients using prescription potassium products is that about two thirds choose to remain on their accustomed regimen without a trial of potassium salt substitutes. Of the remaining one third, I would estimate that one half, after a trial of potassium salt substitutes, choose to remain on the salt substitute; the remainder revert to a prescription product. These estimates are similar to the results reported by Hueston. My impression is that the most likely candidates to remain on salt substitutes are those who are the most compliant with therapy, who abhor the "sick role" the most, and who are cost-conscious. The patients most grateful for the salt substitute option are those who pay the cost of their medications; those with private or state-sponsored prescription plans have little motivation to change to a less expensive, nonprescription product (which may actually *increase* their personal expense).

There is a group of patients, however, who have not used prescription products previously. Many of these patients, when options are described, agree to try the salt substitute. Overall, I would estimate a long-term acceptance rate of 50%. Patients who appreciate the cost savings and who are taking few other medications are the most likely to choose this regimen. Once accustomed to this regimen, it becomes their preferred regimen. Unless expense were an issue, I probably would not offer salt substitutes to a patient taking 12 pills per day. Likewise, patients who request acetaminophen and pseudoephedrine by prescription so their prescription cards will cover the expense will not use potassium salt. This selection process may influence my impression of the long-term acceptability of this regimen.

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The explanation for this differential acceptance is simple. Each of us becomes familiar and comfortable with therapy as it has traditionally been recommended for us. Most physicians are familiar with the difficulties of discontinuing or switching patients' medications. (I know physician-teachers in our specialty who have inherited patients receiving weekly crude liver injections. Developing relationships over years, these physicians have been unable to alter the patients' habits and beliefs.) Hueston's subjects were all pill-takers at the beginning of the study. (We are not told whether they experienced out-of-pocket expense for their medications and whether cost was a consideration for the two who elected to continue to use salt substitutes.) It is not surprising to learn that 80% remained so at the end.

Personally, I "prescribe" salt substitutes as if I were prescribing a drug—I tell patients to consider it as a drug. I prescribe it by brand name (which increases cost minimally, but assures me of relative consistency of 60 mEq potassium per teaspoon) and specific dosage, eg, a measured one-half teaspoon per day. This quantity should be placed in a small personal salt shaker and used during the course of the day—no more, no less. Small salt shakers with snap-on or screw-on moisture-resistant caps are available and are as portable as pill containers. Patients should be warned that some preparations (eg, "lite salt") are a mixture of sodium and potassium salts, and they should be sure to use a potassium-only salt substitute, not a mixture.

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2. Hueston WJ: Use of salt substitutes in the treatment of diuretic-induced hypokalemia. J Fam Pract 1989; 29:623–629

PREPARTICIPATION SPORTS EXAMINATION

To the Editor:

The preparticipation sports examination article by Fields and Delaney (*Fields KB, Delaney M: Focusing the preparticipation sports examination. J Fam Pract 1990; 30:304–312*) covers the traditional examination well, but does not mention any exercise component. For the last eight years, I have included in my office examination and in a school setting examination a 1-mile run.

Murmurs that might be otherwise missed are detected or provoked after exercise. While many of these additional murmurs might not be clinically important, a pulmonary function test after the run is able to detect exercise-induced asthma, which would otherwise be overlooked and is very pertinent to sports participation.

The discussion of exercise-induced asthma suggests using the history to make the diagnosis and yet cites a study showing 11% of Olympic athletes with this condition, one half of whom did not know that they were afflicted. It would seem that failing to detect 5% to 10% of all prospective athletes who do have exercise-induced asthma would be an unacceptable preparticipation examination.

The added advantage of the run is to detect those students who are poorly conditioned. It does seem inconsistent to clear a student for participation with no comment by the physician about the general physical conditioning. The logistics of the run may seem formidable, but it certainly has been possible at either the office or the school.

Another important item is the update of the tetanus immunization. The preparticipation examination is a golden opportunity to give the booster to students who otherwise will graduate and leave home at age 18 years having had their last tetanus shot at age 5 years.

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EXERCISE DURING PREGNANCY

To the Editor:

The article by Robert Jarski and Diane L. Trippet entitled "The Risks and Benefits of Exercise During Pregnancy" (*J Fam Pract 1990; 30:185–189*) represents an excellent review of an important but abstruse subject. For thoroughness of presentation, however, the guidelines developed by the American College of Obstetricians and Gynecologists (*Exercise During Pregnancy and the Postnatal Period*, Washington, DC, ACOG, 1985) should have been referenced and discussed. There is considerable disagreement among experts in the field of obstetrics-gynecology and sports medicine, and for completeness these points should have been made in the article.

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The preceding letter was referred to Dr Jarski and Ms Trippett, who respond as follows:

We thank Dr Birrer for his comments and for calling readers' attention to the ACOG guidelines. Our article was principally limited to original data in articles identified through our MEDLINE literature search. Additional information can only help physicians in making their prescription decisions. Our recommendations are not completely contradictory, and we concur with the statement at the end of the 1985 ACOG paper: "It does not dictate an exclusive course of treatment or procedure to be followed and should not be construed as excluding other acceptable methods of practice."

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