Somatization disorder

MARK W. KETTERER, PhD
CHARLES D. BUCKHOLTZ, DO

Somatization disorder (SD) is a syndromatic classification that allows a physician to identify more easily patients with a lifelong history of chronic subjective physical complaints that are unverified by objective examinations either at the time of initial presentation or during the subsequent five years. The somaticizing process is believed to be an expression of emotional distress. The most common complaints of SD patients include recurrent pain (site and quality vary), conversion (pseudoneurologic) symptoms, nervousness or depression (or both), sexual and marital discord, and, often, menstrual difficulties. Such patients will generally have a history of repeated hospitalization or surgery. These symptoms are not perceived as mild or unimportant but lead to physician consultation, prescription drug use, and modification of life-style. Such patients are prone to "doctor-shopping" and self-medication and are at risk for many iatrogenic illnesses. Because they generally are resistant to psychologic explanations for their condition, management aimed at protecting them from the consequences of their behavior is important. A heightened threshold for instituting aggressive diagnostic and treatment procedures is necessary.

Because of medicine's strong biologic orientation¹ and its roots in Euro-American culture, disorders that encompass the mind-brain/body dichotomy can be uniquely problematic in primary care settings.²⁻⁴ The mind-brain duality advocated by René Descartes in the 17th century^{5,6} still dominates the way most educated people conceptualize the relationship between psychologic events and physiologic processes, despite powerful evidence that psychologic phenomena are nothing more, or less, than concomitants of CNS activity.⁷

The Cartesian version of psychoneural relationships has been heuristic in that it has allowed medical science to take on manageable research and clinical tasks rather than being overwhelmed by the

full complexity of human pathophysiology, as occurred prior to the late 1800s.⁸

Unfortunately, the same set of beliefs can blind practitioners to the role of psychologic processes in generating complaints of physical symptoms. One set of disorders that often confuses mind-brain/body relationships for the primary care physician are the somatoform disorders.

A patient who chronically reports one or more subjective physical symptoms that cannot be verified by objective evidence has a somatoform disorder. This category includes conversion disorder, somatoform pain disorder, hypochondriasis, body dysmorphic disorder, and somatization disorder.⁹ The term somatoform suggests that the patient's illness has the appearance (or form) of a physical disorder. However, the common feature of somatoform disorders is that there is no demonstrable evidence of organic dysfunction or no known physiologic mechanism for explaining the patient's symptoms, and that there is a reasonable basis for presuming causality by psychologic factors.

It must be remembered that unlike the factitious disorders or malingering, the production of symptoms is not intentional or conscious. Yet the production of symptoms, upon close and detailed scrutiny, almost always will appear to be controlled or influenced by psychosocial consequences.

Although not generally classified as somatoform disorders, traditional psychiatric syndromes, including depression and the anxiety disorders, frequently will be manifested as physical complaints^{10,11} and, thus, they arguably can be so categorized. This is because of the patient's denial (repression, suppression, or misattribution) of psychologic problems, the automatization of cognitive and behavioral coping strategies,⁷ and the attendant physical symptoms of these disorders (fatigue and preoccupation with minor pains in depression, or palpitations, dizziness, dyspnea, or diaphoresis in panic attack).

The best understood of the somatoform disorders is somatization disorder (SD).¹²⁻¹⁴

Terminology

Because the term hysteria has come to be applied to a personality style,^{15,16} a personality disorder,^{9,17} an acute emotional state, and a mental disorder,¹²

recent empiric studies have begun using more concrete criteria and a different terminology to clarify meaning. For example, the personality disorder, which is characterized by overly dramatic, reactive, and intensely expressed behavior and disturbances in interpersonal relationships, now is termed "histrionic."⁹ The mental disorder has come to be known as Briquet's syndrome (after the physician who first described a polysymptomatic patient with a complicated medical history who was not objectively ill¹⁸) or SD.

Epidemiology and demographics

The prevalence of SD among women in the United States is 0.2% to 2%.⁹ Somatization disorder is rarely diagnosed in men. However, on the basis of one study,¹⁹ SD was a frequent finding in a primary care outpatient setting. The authors speculate that "...for the average physician, this diagnosis could be made nearly every day that patients are seen."

Available data indicate that SD is a familial disorder. First-degree female relatives of SD patients have a much higher rate of SD (about 10% to 20%) than would be expected in the general population.²⁰⁻²⁴ Additionally, male relatives of SD patients have much higher rates of antisocial personality disorder and psychoactive substance abuse than seen in the general population.²⁰⁻²⁵

Etiology

The presence of a familial factor in the background of SD patients is consistent with both a genetic and environmental etiology.²⁶ As with the other somatoform disorders, it is presumed that unconscious secondary gain (the social consequences of being ill, including decreased expectations of others for work and increased attention) plays a major role in initiating and maintaining the symptomatic picture. That is, patients unknowingly have learned to cope with their own emotional needs (attention, fatigue, loneliness, anger) by becoming "ill"²⁷—a strategy that they likely observed was used by their mother, sister, aunt, or grandmother.

Such a coping strategy allows an individual to obtain something they need without having to take interpersonal responsibility for asking overtly. This strategy presumably is adaptive in an interpersonal environment with multiple antisocial, personality-disordered men and multiple "sick" women.⁷

The patient, it must be emphasized, is unaware that her illnesses serve these psychosocial purposes, and she is highly resistant to any such suggestion. The resistance is assumed to be a product of the unconscious nature of the psychologic mechanism,⁷ fear of stigmatization ("It's all in your

head"), and the unconsciously perceived consequence (interpersonal confrontation) of acknowledging the anger, sadness, or other emotion.

Natural history and course

The onset of chronic physical complaints and symptoms generally occurs prior to age 30, most often in the second decade of life. The course of the illness generally is either chronic or intermittent. The disorder rarely remits spontaneously; careful history-taking will reveal that seldom does a year pass without the patient seeking some form of medical attention. In a severe case, the patient will be an invalid and will squander her life in a preoccupation with physicians, medications, and symptoms. Psychosocial stressors often appear to be the precipitating event, despite the patient's denial of their relevance. Interestingly, the disorder does not appear to manifest in childhood. It is unknown whether such patients display a propensity for school avoidance or other forms of secondary gain as children.

Signs and symptoms

SD is characterized by recurrent, multiple physical complaints that cannot be objectively verified but that have led to physician consultation, use of a prescription medication, modification of life-style to accommodate the symptom, or a combination of these. While the list of symptoms SD patients will endorse is endless, most common are recurrent pain (although site and quality vary), conversion (pseudoneurologic) symptoms, nervousness or depression (or both), sexual and marital discord, and repeated hospitalization or surgery.

One early study²⁸ listed the astonishing frequency of various signs and symptoms in a group of SD patients (Table 1). A more recent study²⁹ reported that SD patients report more physical symptoms than objectively ill patients (with chronic obstructive pulmonary disease or diabetes) while reporting only slightly more psychologic symptoms (Fig 1).

Diagnosis

Because of the vague and variable nature of presentation, the physician is likely to find history-taking a confusing process with SD patients. A straightforward, sequential history of a principal complaint is almost impossible to obtain. Patients frequently will contradict themselves, and, if confronted about such inconsistencies, they will confabulate at least a marginally plausible explanation.

In trying to reduce the confusion, many physicians latch onto a single symptom to guide treat-

*Evidence directly linking
elevated cholesterol and CAD
made you take a closer look
at lipid levels*

**BUT THERE'S
MORE...**

Lorelco is indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia, as an adjunct to diet.

LOWERING ELEVATED MAY BE JUST

Lorelco (probucol) offers proven long- term cholesterol- lowering efficacy*

- Lowers total cholesterol by up to 27%^{1,2}
- Maintains lower levels as proven over a 12-year period³
- Increases fractional rate of LDL catabolism
(See Clinical Pharmacology)

* The effect of probucol-induced reduction of serum cholesterol or triglyceride levels or reduction of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

Recent in vitro studies and human and/or animal in vivo data suggest unique modes of action†

Inhibits the oxidative modification of LDL⁴⁻¹⁰

- Modified (cytotoxic) LDL may play a role in foam cell formation⁴⁻¹⁰
—foam cell formation is an initial step in atherosclerotic plaque development⁴⁻¹⁰
- Inhibits development of atherosclerotic lesions in animals^{6,8}

†Data are only used to explain the unique modes of action of Lorelco; no clinical benefit is implied.

Lorelco is not an innocuous drug and strict attention should be paid to the Indications, Contraindications, Warnings, and Precautions sections of Prescribing Information.

References: 1. *S Afr Med J* 1982;62:7-11. 2. *Arch Intern Med* 1981;141:1428-1432. 3. Data on file, MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242-9553. 4. *Am J Cardiol* 1988;62:31B-36B. 5. *Atherosclerosis* 1986;62:209-217. 6. *Proc Natl Acad Sci USA* 1987;84:5928-5931. 7. *J Clin Invest* 1986;77:641-644. 8. *Proc Natl Acad Sci USA* 1987;84:7725-7729. 9. *Am J Cardiol* 1988;62:6B-12B. 10. *Am J Cardiol* 1986;57:16H-21H. 11. *Am J Cardiol* 1988;62:57B-59B. 12. *Am J Cardiol* 1988;62:66B-72B. 13. *Am J Cardiol* 1988;62:73B-76B. 14. *Am J Cardiol* 1988;62:52B-56B. 15. *Appl Pathol* 1983;1:89-96. 16. *Proc Soc Exp Biol Med* 1971;136:1216-1221. 17. *Jpn J Pharmacol* 1986;41:211-222. 18. *Am J Cardiol* 1986;57:29H-35H.

LEVELS THE BEGINNING

LORELCO[®]

PROBUCOL

Recent in vitro studies and human and/or animal in vivo data suggest unique modes of action†

Enhances HDL-mediated reverse cholesterol transport §3,11-14

- Lorelco has been shown to regress atherosclerotic lesions in animals ‡15-17
- The effects of probucol on HDL-cholesterol may reflect improved dynamics of HDL-mediated reverse cholesterol transport //3,12,14,18

‡See Contraindications, Warnings, and Animal Pharmacology and Toxicology.

§These effects of probucol on LDL (increase in catabolic rate) and HDL-cholesterol may be linked to the observed increased excretion of fecal bile acids, a final metabolic pathway for elimination of cholesterol from the body. (See Clinical Pharmacology.)

LORELCO[®]

PROBUCOL 500

500 mg tablets b.i.d. with meals

TAKES YOU TO THE NEXT LEVEL OF CHOLESTEROL CONTROL

//The probable benefits obtained from LDL-cholesterol reduction must be weighed against the possible risk of a reduction in HDL-cholesterol when assessing the response of patients to probucol. If satisfactory lipid alteration is not achieved, the drug should be discontinued. (See Precautions.)

See Prescribing Information appearing on next page.

Merrell Dow U.S.A.

Lorelco® Tablets (probuco)

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION: Lorelco (probuco) film-coated tablets for oral administration contain 250 mg or 500 mg of probuconol per tablet. Each tablet also contains as inactive ingredients: corn starch, ethylcellulose, glycerin, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2910, iron oxide, lactose, magnesium stearate, microcrystalline cellulose, polyisobutylene, talc, and titanium dioxide. Lorelco is an agent for the reduction of elevated serum cholesterol. The chemical name is 4,4'-[1,1-bis(4-ethylphenyl)]bis[2,6-bis(1,1-dimethyl-4-ethylphenyl)]sulfone. Its chemical structure does not resemble that of any other available cholesterol-lowering agent. It is lipophilic.

CLINICAL PHARMACOLOGY: Lorelco lowers total serum cholesterol and has relatively little effect on serum triglycerides. Patients responding to probuconol exhibit a decrease in low-density lipoprotein (LDL) cholesterol. Cholesterol is reduced not only in the LDL fraction, but also in the high-density lipoprotein (HDL) fraction with proportionately greater effect on the high-density portion. Epidemiologic studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease. The risk of lowering HDL-cholesterol while lowering LDL-cholesterol remains unknown. There is little or no effect reported on very low-density lipoprotein (VLDL).

Studies on the mode of action of Lorelco indicate that it increases the fractional rate of LDL catabolism. This effect may be linked to the observed increased excretion of fecal bile acids, a final metabolic pathway for the elimination of cholesterol from the body. Lorelco also exhibits inhibition of early stages of cholesterol biosynthesis and slight inhibition of absorption of dietary cholesterol. There is no increase in the cyclic precursors of cholesterol, namely desmosterol and 7-dehydrocholesterol. On this basis, it is concluded that Lorelco does not affect the later stages of cholesterol biosynthesis.

Absorption of Lorelco from the gastrointestinal tract is limited and variable. When it is administered with food, peak blood levels are higher and less variable. With continuous administration in a dosage of 500 mg b.i.d., the blood levels of an individual gradually increase over the first three to four months and thereafter remain fairly constant. In 116 patients treated with Lorelco for periods of three months to one year, the mean blood level was 23.6 ± 17.2 mcg/mL ($\pm$ S.D.) ranging to 78.3 mcg/mL. Levels observed after seven years of treatment in 40 patients yielded an average value of 21.5 ± 16.5 mcg/mL ($\pm$ S.D.) ranging to 62.0 mcg/mL. In a separate study in eight patients, blood levels averaged 19.0 mcg/mL at the end of 12 months of treatment. Six weeks after cessation of therapy, the average had fallen by 60%. After six months, the average had fallen by 80%.

In December 1984, a National Institutes of Health Consensus Development Conference Panel¹ concluded that lowering definitely elevated blood cholesterol levels (specifically blood levels of LDL-cholesterol) will reduce the risk of heart attacks due to coronary heart disease. The effect of probuconol-induced reduction of serum cholesterol or triglyceride levels, or reduction of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

INDICATIONS AND USAGE: Serious animal toxicity has been encountered with probuconol. See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections. Probuconol is not an innocuous drug and strict attention should be paid to the INDICATIONS, CONTRAINDICATIONS, and WARNINGS.

Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight may be an important factor and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory disease such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision ultimately is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

The selection of patients for cholesterol-lowering drug therapy should take into account other important coronary risk factors such as smoking, hypertension, and diabetes mellitus. Consideration should be given to the efficacy, safety, and compliance factors for each of the cholesterol-lowering drugs prior to selecting the one most appropriate for an individual patient.

Lorelco may be indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (Types IIa and IIb hyperlipoproteinemia),² whose elevated LDL-cholesterol has not responded adequately to diet, weight reduction, and control of diabetes mellitus. Lorelco may be useful to lower elevated LDL-cholesterol that occurs in those patients with combined hypercholesterolemia and hypertriglyceridemia (Type IIb) due to elevation of both LDL and VLDL, but it is not indicated where hypertriglyceridemia is the abnormality of most concern. After establishing that the elevation in serum total cholesterol represents a primary lipid disorder, it should be determined that patients being considered for treatment with Lorelco have an elevated LDL-cholesterol as the cause for an elevated total serum cholesterol. This may be particularly relevant for patients with elevated triglycerides and with markedly elevated HDL-cholesterol values, where non-LDL fractions may contribute significantly to total cholesterol levels without apparent increase in cardiovascular risk. In most patients, LDL-cholesterol may be estimated according to the following equation:

$$\text{LDL-cholesterol} = \text{Total cholesterol} - [(0.16 \times \text{triglycerides}) + \text{HDL-cholesterol}]$$

When total triglycerides are greater than 400 mg/dL, this equation is less accurate. In such patients, LDL-cholesterol may be obtained by ultracentrifugation.

It is not always possible to predict from the lipoprotein type or other factors which patients will exhibit favorable results. Lipid levels, including HDL-cholesterol, should be periodically assessed.

The effect of probuconol-induced reduction of serum cholesterol or triglyceride levels, or reduction of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

CONTRAINDICATIONS: (See also WARNINGS and PRECAUTIONS.) Lorelco is contraindicated in patients who are known to have a hypersensitivity to it. Lorelco is contraindicated in patients with evidence of recent or progressive myocardial damage or findings suggestive of serious ventricular arrhythmias or with unexplained syncope or syncope of cardiovascular origin.

WARNINGS: SERIOUS ANIMAL TOXICITY HAS BEEN ENCOUNTERED WITH PROBUCONOL IN RHESUS MONKEYS FED AN ATHEROGENIC DIET AND IN BEAGLE DOGS. (See ANIMAL PHARMACOLOGY AND TOXICOLOGY SECTION.)

Prolongation of the QT interval can occur in patients on Lorelco. Serious arrhythmias have been seen in association with an abnormally long QT interval in patients on Lorelco alone and in patients on Lorelco and a concomitant antiarrhythmic drug. The following precautions are deemed prudent.

1. Patients should be advised to adhere to a low cholesterol, low fat diet at the start of treatment with Lorelco and throughout the treatment period.
2. An ECG should be done prior to starting treatment and repeated at appropriate intervals during treatment. If an abnormally long QT interval is observed, the possible benefits and risks should be carefully considered before making a decision to continue Lorelco.

Lorelco therapy should be discontinued or not started if the QT interval at an observed heart rate on a resting ECG is persistently more than one of the values listed below:

Observed Heart Rate (beats/min)	QT Interval in sec (15% above the upper limit of normal)*	
	Males	Females
40	0.56	0.58
50	0.52	0.53
60	0.49	0.50
70	0.45	0.47
80	0.43	0.44
86	0.42	0.43
92	0.40	0.41
100	0.39	0.40
109	0.37	0.38
120	0.36	0.36
133	0.34	0.35

*Values calculated from Burch GE, Winsor T. A primer of electrocardiography. Philadelphia, PA: Lea and Febiger; 1958; p. 272 (Table 6).

3. Patients developing unexplained syncope or syncope of cardiovascular origin should have Lorelco therapy discontinued and should have ECG surveillance.
4. Drugs that prolong the QT interval are more likely to be associated with ventricular tachycardia after:
 - a. An increase in the dose of the drug.
 - b. Addition of a second drug that prolongs the QT interval (including tricyclic antidepressants, class I and III antiarrhythmics, and phenothiazines).
 - c. Hypokalemia or hypomagnesemia.
 - d. Severe bradycardia due to intrinsic heart disease or drug effects on the atrial rate (beta-blockers) or AV block (digoxin).
 - e. Development of recent or acute myocardial infarction, ischemia, or inflammation.

The use of Lorelco in patients receiving any of these drugs should be based on the conclusion that alternate methods of hypocholesterolemic therapy are either ineffective or not tolerated, and the potential benefits of cholesterol lowering outweigh the risk of serious arrhythmia.

The following conditions should be resolved or corrected prior to initiation of therapy with Lorelco:

- a. Hypokalemia
- b. Hypomagnesemia
- c. Severe bradycardia due to intrinsic heart disease or drug effects on the atrial rate (beta-blockers) or AV block (digoxin).
- d. Recent or acute myocardial infarction, ischemia, or inflammation.

PRECAUTIONS

General: Before instituting therapy with Lorelco, adequate baseline studies should be performed to determine that the patient has persistently elevated total and LDL-cholesterol levels representing a primary lipid disorder, and that the increased cholesterol is not due to secondary conditions such as hypothyroidism, poorly controlled diabetes mellitus, obstructive liver disease, nephrotic syndrome, or dysproteinemias. Serum lipid levels, including LDL-cholesterol, should be determined after an overnight fast before treatment, during an adequate trial of diet and weight reduction therapy prior to addition of drug therapy, and periodically during combined diet and drug therapy, including assessment during the first several months of drug treatment. A favorable trend in lipid levels should be evident during the first three to four months of administration of Lorelco, and if satisfactory lipid alteration is not achieved, the drug should be discontinued. Lorelco lowers serum total and LDL-cholesterol, and also lowers HDL-cholesterol in most patients with elevated LDL-cholesterol. Epidemiologic studies within hypercholesterolemic populations have shown that serum HDL-cholesterol is an independent, inversely correlated, risk factor for coronary heart disease (see CLINICAL PHARMACOLOGY). Human studies which will attempt to confirm or deny the hypothesis that drug-induced alteration in HDL-cholesterol affects cardiovascular risk are currently under evaluation. It is not known whether Lorelco-induced reduction of serum HDL-cholesterol will offset cardiovascular risk since no long-term, controlled clinical trials of Lorelco for the prevention of coronary heart disease, similar to the LRC-CPPPT (see CLINICAL STUDIES), have been performed. The probable benefits obtained from LDL-cholesterol reduction must be weighed against the possible risk of a reduction in HDL-cholesterol when assessing the response of each patient receiving Lorelco treatment. If satisfactory lipid alteration is not achieved, the drug should be discontinued.

Information for Patients: The patient should be instructed to adhere to a prudent diet. Females should be cautioned against becoming pregnant for at least six months after discontinuing Lorelco and should not breast-feed their infants during the use of Lorelco.

Laboratory Tests: The physician should schedule periodic blood lipid determinations and periodic ECGs. (See WARNINGS.) Elevations of the serum transaminases (SGOT, SGPT), bilirubin, alkaline phosphatase, creatine phosphokinase, uric acid, blood urea nitrogen, and blood glucose above the normal range were observed on one or more occasions in various patients treated with Lorelco. Most often these were transient and could have been related to the patient's clinical state or other mode of therapy. Although the basis for the relationship between Lorelco and these abnormalities is not firm, the possibility that some of these are drug related cannot be excluded. In controlled trials, the incidence of abnormal laboratory values was no higher in patients treated with Lorelco than in the patients who received placebo. If abnormal laboratory tests persist or worsen, or if clinical signs consistent with the abnormal laboratory tests develop, or if systemic manifestations occur, Lorelco should be discontinued.

Drug Interactions: The addition of clofibrate to Lorelco is not recommended, since the lowering effect on mean serum level of either LDL or total cholesterol is generally not significantly additive and, in some patients, there may be a pronounced lowering of HDL-cholesterol.

Neither oral hypoglycemic agents nor oral anticoagulants alter the effect of Lorelco on serum cholesterol. The dosage of these agents is not usually modified when given with Lorelco.

Monkeys fed a high fat, high cholesterol diet admixed with probuconol exhibited serious toxicity (See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections.) Prolongation of the QT interval can occur in patients on Lorelco and serious arrhythmias have been seen in association with an abnormally long QT interval in patients on Lorelco. The addition of a second drug that prolongs the QT interval (including tricyclic antidepressants, class I and III antiarrhythmics, and phenothiazines) increase the risk of serious arrhythmia. (See CONTRAINDICATIONS AND WARNINGS.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In chronic studies of two years' duration in rats, no toxicity or carcinogenicity was observed. These results are consistent with the lack of any adverse effect on fertility and the negative findings in tests for mutagenic activity in rats.

Pregnancy

Teratogenic Effects

Pregnancy—Category B: Reproduction studies have been performed in rats and rabbits at doses up to 50 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus due to probuconol. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Furthermore, if a patient wishes to become pregnant, she should be advised to discontinue therapy with Lorelco. (See CLINICAL PHARMACOLOGY.)

Labor and Delivery: The effect of Lorelco on human labor and delivery is unknown.

Nursing Mothers: It is not known whether this drug is excreted in human milk, but it is likely, since such excretion has been shown in animals. It is recommended that nursing not be undertaken while a patient is on Lorelco.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Gastrointestinal

diarrhea or loose stools, flatulence, abdominal pain, nausea, vomiting, indigestion, gastrointestinal bleeding

Cardiovascular

prolongation of the QT interval on ECG, syncope, ventricular arrhythmias (ventricular tachycardia, torsades de pointes, ventricular fibrillation), sudden death

Neurologic

headache, dizziness, paresthesia, insomnia, tinnitus, peripheral neuritis

Hematologic

ecchymosis, low hemoglobin and/or hematocrit, thrombocytopenia

Dermatologic

rash, pruritus, ecchymosis, petechiae, hyperhidrosis, fisted sweat

Genitourinary

impotency, nocturia

Ophthalmic

conjunctivitis, tearing, blurred vision

Endocrine

enlargement of multinodular goiter

Idiosyncrasies

observed with initiation of therapy and characterized by dizziness, palpitations, syncope, nausea, vomiting and chest pain

Other

diminished sense of taste and smell, anorexia, angioneurotic edema

DRUG ABUSE AND DEPENDENCE: No evidence of abuse potential has been associated with Lorelco, nor is there evidence of psychological or physical dependence in humans.

OVERDOSEAGE: There is a single report of a 15-kg, three-year-old, male child who ingested 5 g of probuconol. Emesis was induced. The child remained well, apart from a brief episode of loose stools and flatulence. No specific information is available on the treatment of overdose with Lorelco and no specific antidote is available. Probuconol is not dialyzable. Treatment is symptomatic and supportive. Probuconol has shown no identifiable acute toxicity in mice and rats. In the animals the LD₅₀ (oral) is in excess of 5 g/kg of body weight.

DOSEAGE AND ADMINISTRATION: For adult use only. The recommended and maximal dose is 1000 mg daily given in two divided doses of 500 mg each (two 250 mg tablets or one 500 mg tablet) with the morning and evening meals.

HOW SUPPLIED: 250 mg round, white, film-coated tablets imprinted with either the DOW diamond trademark over code number 51 or LORELCO 250. Bottles of 120 (NDC 068-0051-52)

500 mg capsule-shaped, white, film-coated tablets, marked LORELCO 500. Bottles of 100 (NDC 068-0053-61)

Keep well closed. Store in a dry place. Avoid excessive heat. Dispense in well-closed light-resistant containers with child-resistant closures.

ANIMAL PHARMACOLOGY AND TOXICOLOGY: In rhesus monkeys, administration of probuconol in diets containing unusually high amounts of cholesterol and saturated fat resulted in the death of four of eight animals after several weeks. Premortem studies of these monkeys showed that those obtained in the placebo group treated with diet alone (30% cholesterol) were 50% longer than those observed in untreated monkeys. Serum levels of probuconol greater than 20 mcg/mL were generally associated with some prolongation of the QT interval in the cholesterol-fed monkey. A 75 mcg or greater increase in QT interval from control values was usually seen at 40 mcg/mL and above. Blood levels in humans receiving Lorelco average approximately 20 mcg/mL and not uncommonly reach levels of 40 mcg/mL and higher. Rhesus monkeys fed normal (low fat) chow diets receiving probuconol three to thirty times the human dose equivalent achieved blood levels only one-third those of many human subjects. No adverse effects were detected in these monkeys over an eight-year period of continuous drug administration.

In another study in rhesus monkeys, an atherogenic diet was fed for two years and daily treatment with probuconol, separated in time from the atherogenic meal, was carried out during the second year. Serum probuconol levels ranged 20 to 50 mcg/mL in five of monkeys, and less in the remaining animals. Marked prolongation of the QT interval in the ECG or syncope behavior was not observed over the entire one-year treatment period. Regression of gross aortic lesions comparable to that observed in a parallel group of monkeys receiving cholestyramine was seen in animals receiving probuconol. It should be emphasized that both HDL-cholesterol and LDL-cholesterol were markedly reduced in this regression study. During the performance of a two-year chow study involving 32 probuconol-treated dogs (beagles), there were 12 fatalities.

Subsequent experiments have indicated that probuconol sensitizes the canine myocardium to epinephrine, resulting in ventricular fibrillation in many dogs. Among the animal species in which probuconol has been studied, the dog is peculiar with respect to phenomenon of sudden death due to the sensitization of the myocardium to epinephrine. In contrast to findings in the dogs, injections of epinephrine to probuconol-treated monkeys did not induce ventricular fibrillation.

In other studies, monkeys were given probuconol either before and after, or only after myocardial infarction was induced by coronary artery ligation. In these studies, there was no difference between probuconol- and placebo-treated groups with respect to either survival or detailed blind quantitation of myocardial changes (gross and histopathologic).

Probuconol has shown no identifiable toxicity in mice and rats. In these animals, the LD₅₀ (oral) is in excess of 5 g/kg of body weight. In chronic studies of two years' duration in rats, no toxicity or carcinogenicity was observed.

From studies in rats, dogs, and monkeys, it is known that probuconol accumulates slowly in adipose tissue. Approximately 90% of probuconol administered orally is unabsorbed. For that which is absorbed, the biliary tract is the major pathway for clearance from the body and very little is excreted by way of the kidneys.

Myocardial injury was produced in various groups of rats by one of the following procedures: aortic coarctation, coronary ligation, or cobalt or isoproterenol injection. After probuconol administration, no deleterious effects related to treatment occurred as measured by survival and microscopic examination of myocardial damage.

Probuconol was administered to minipigs beginning ten days before ligation of coronary artery and continued for 60 days after surgery. Challenge with epinephrine at the end of 60 days failed to induce ventricular fibrillation in any of the coronary-ligated probuconol-treated minipigs.

CLINICAL STUDIES: In a multicenter, randomized, double-blind study, the LRC-CPPPT³ hypercholesterolemic patients treated with an oral bile acid sequestrant (cholestyramine) and a cholesterol-lowering diet experienced average total and LDL-cholesterol reductions greater than those obtained in the placebo group treated with diet alone. The cumulative seven-year incidence of the primary end point—combined incidence of definite CHD death and/or definite nonfatal myocardial infarction—was 7% in the cholestyramine group and 8.6% in the placebo group. This was a 19% reduction in risk (P less than 0.05, single tail test) of the primary end point reflecting a 24% reduction in definite CHD death and a 19% reduction in nonfatal myocardial infarction.

The subjects included in the study were middle-aged men (35-59 years old) with serum cholesterol levels at least 265 mg/dL and no previous history of heart disease. It is not clear to what extent these findings can be extrapolated to other segments of the hypercholesterolemic population not studied.

The bile acid sequestrant, cholestyramine, was used in the above trial. Caution should be exercised in extrapolating these results to Lorelco since it differs from cholestyramine with regard to its mode of action, spectrum of cholesterol-lowering potential, effect on HDL-cholesterol, and possible toxicity. The effect of probuconol-induced reduction of serum cholesterol levels on morbidity or mortality due to coronary heart disease has not been established.

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TABLE 1. FREQUENCY OF SIGNS AND SYMPTOMS ENDORSED BY SOMATIZATION DISORDER (SD) PATIENTS (ADAPTED FROM PERLEY AND GUZE²⁸).

SD patients endorsing (%)	Sign/symptom	SD patients endorsing (%)	Sign/symptom
92	Nervousness	44	Aphonia
88	Back pain		Dysuria
84	Joint pain		Sexual indifference
	Extremity pain		Had to quit working because felt bad
	Dizziness	40	Always sickly (most of life)
	Fatigue	36	Other bodily pain
	Weakness		Wanted to die
80	Headaches	32	Anesthesia
	Nausea		Vomiting
	Abdominal pain	28	Lump in throat
72	Dyspnea		Weight loss
	Trouble doing anything because felt bad		Burning pains in rectum, vagina, or mouth
	Chest pain		Felt life was hopeless
68	Abdominal bloating		Thought of suicide
64	Visual blurring	24	Frigidity (absence of orgasm)
	Anxiety attacks	20	Blindness
	Constipation		Fits or convulsions
	Depressed feelings		Diarrhea
60	Palpitations		Vomiting all nine months of pregnancy
	Anorexia	16	Unconsciousness
	Crying spells		Olfactory hallucination
56	Fainting		Sudden fluctuations in weight
52	Dyspareunia	12	Paralysis
48	Food intolerances		Visual hallucination
	Dysmenorrhea (other than during pregnancy or premarital)		Attempted suicide
	Menstrual irregularity	8	Amnesia
	Excessive menstrual bleeding		Urinary retention
	Phobias		Dysmenorrhea (pregnancy only)
	Thought of dying	4	Deafness
			Dysmenorrhea (premarital only)

Fig 1. Average mental health and physical functioning scores of 41 SD patients on the Rand Health Status Measures compared to general population norms and a medically ill (chronic obstructive pulmonary disease and diabetes) sample (data adapted from Smith and associates²⁹).

ment; at best, they are temporarily successful.³⁰⁻³² An SD patient will "develop" symptoms in which the physician shows most interest. For example, if the physician is a gastroenterologist, gastroin-

testinal symptoms will predominate in the clinical picture; with a cardiologist, chest pain is a likely complaint. Such patients seem unconsciously, although exquisitely, responsive to the physician's

Fig 2. Frequency of operations for SD (hysteria), medically ill, and healthy control subjects as a function of age (data adapted from Cohen and coworkers³³).

most subtle nonverbal communication of interest.

A good standard question to ask oneself in understanding and managing such patients is: "Why this complaint, and why now?" A thorough understanding of the patient's psychosocial history, interpersonal environment, and events temporally related to the onset of the latest symptoms will provide the practitioner with the raw data on which a psychodynamic explanation can be constructed and predictions about the future course can be based.

Because of the physician's well-intentioned attempts to help, the SD patient is at risk for recurrent multiple exploratory or "therapeutic" surgeries.³³ Many will develop "gridiron abdomen" from the many surgical scars, and many undergo more operations than verifiably ill patients (Fig 2).³³ (In the most dramatic case known to us, a 34-year-old woman was evaluated at the request of a surgical resident. She was undergoing a workup for her 14th exploratory laparoscopy in 16 years. The sole reason for the current laparoscopy was continued unexplained abdominal pain. All laboratory and radiologic findings were normal. Consultation with the attending surgeon and referring physician led to cancellation of the operation. The physician reported feeling pressured to "do something" with the patient and therefore referred her for diagnostic surgery to "reassure" her.)

Somatization disorder has been demonstrated to be a unique and clinically useful nosologic category.^{34,35} In the original studies testing the prog-

nostic utility of SD, five-year follow-up of patients whose condition originally was diagnosed as conversion or hysteric reactions revealed that 50% later were found to have true medical illness, which probably caused the original symptomatic picture.^{28,36} By using the original SD criteria,^{28,34-39} the probability of such an outcome is reduced to 10%^{12,35}; that is, 90% of patients meeting the original criteria (82% of those meeting the DSM III criteria) will not have medical illness develop but will remain objectively healthy over the ensuing five years.

The original criteria^{28,34-39} required 25 symptoms spread across nine of ten body systems. The requirement for wide systemic spread was based originally on the premise that any true physical disease, even if subclinical, most likely would be limited to one or a few systems. But reevaluation of the initial data has revealed that a higher degree of diagnostic sensitivity is accomplished, with no real loss of specificity, by requiring 13 positive symptoms and dropping the requirement of spread across body systems.⁹ Several checklists⁴⁰⁻⁴⁴ exist to aid the primary care practitioner in diagnosing the somatization disorder. But the currently accepted diagnostic criteria are contained in Table 2.⁹

The practitioner always must be alert to the possibility of an organic cause for the patient's discomfort. Other psychologic disorders also must be considered in the differential diagnosis. These include, but are not limited to, anxiety disorders (especially those characterized by recurrent panic attacks), schizophrenia with multiple somatic delusions, conversion disorders, depression with somatic presentation, and factitious disorder with physical symptoms (Münchhausen syndrome).

Two useful axioms for the practitioner to remember are that no psychiatric sign or symptom is pathognomonic of a psychiatric disorder, and that no physical sign or symptom is pathognomonic of a medical disorder. The practitioner who can incorporate these principles into his or her habitual way of conceptualizing patients may prevent the incorrect treatment of medical illnesses as psychologic disorders and psychologic disorders as medical ailments.

Complications

Many of the most serious complications of SD are iatrogenic. Aggressive, well-intended attempts of multiple physicians to diagnose and treat various symptoms places the patient at risk for the routine complications of surgery (anesthetic-induced sudden death, infection, adhesions) and abuse of psychoactive substances (analgesics, soporifics, anxiolytics, antidepressants). Data indicate that SD

patients expend up to 14 times as much as the general population on physician services and nine times as much on total health care.¹⁹

SD patients generally have chaotic work histories⁴⁵ because they differ with employers about time off from work for bed rest and physician visits (an average of seven days a month are missed for illness²⁹), abuse of insurance coverage (average medical bill of \$4,700 per year²⁷), and a lesser work load because of weakness, fatigue, and illness. Similar conflicts will arise with spouses and offspring, who alternately feel resentment at or compassion for the patient's suffering. As the patient's history unfolds, significant others come to perceive themselves as manipulated or abused by the patient. Sexual avoidance or dysfunction is common among these patients and is another source of marital strain.

Occasionally, SD patients experience depressive symptoms of sufficient severity to cause incapacity. As with any depressed patient, suicidal potential must be monitored continually. Foreseeable interpersonal crisis must be the focus of counseling to minimize the probability of suicide attempts.

Management and treatment

Somatization disorder patients often evoke frustration in physicians because these patients are viewed as not really sick and therefore in violation of the implicit physician-patient social compact. To help protect these patients from their own harmful proclivities, the primary care physician must recognize that the behavior is directed entirely unconsciously. Because patients are unable or unwilling to consider psychogenic explanations, they can not attribute causality of their distress to psychosocial events.⁴⁶ Even the most subtle display of frustration or direct challenge to the validity (reality) of the patient's illness is counterproductive and most likely will lead to the patient seeking help elsewhere.

It is imperative that the physician presents a sympathetic demeanor. Regularly scheduled visits will reduce the patient's need to create symptoms. Physical examinations can reassure the patient that complaints are being taken seriously. Routine screening tests (fasting urine glucose tests, serum lipid determinations, Papanicolaou smears, mammograms) conducted when appropriate and when the patient is most demanding and distressed can both reassure the patient of the physician's concern and detect malignant conditions in their early phases.

Not only is it possible for such patients to have objectively verifiable (real) illnesses develop, but such patients are, in fact, suffering, and they are

TABLE 2. DIAGNOSTIC CRITERIA FOR SOMATIZATION DISORDER (ADAPTED FROM SPITZER⁹).

(A) A history of many physical complaints or a belief that one is sickly, beginning before the age of 30 and persisting for several years.

(B) At least 13 symptoms from the list below. To count a symptom, the following criteria must be met: No organic pathologic findings or, when there is related organic disease, the complaint or resulting social or occupational impairment is grossly in excess of what would be expected from the physical findings; the symptom has not occurred only during a panic attack; and the symptom has caused the patient to take medicine (other than over-the-counter pain medication), visit a doctor, or alter life-style.

Symptom list

- Gastrointestinal symptoms:
 - Vomiting (other than during pregnancy) *
 - Abdominal pain (other than when menstruating)
 - Nausea (other than motion sickness)
 - Bloating (gaseous)
 - Diarrhea
 - Intolerance for several different foods
- Pain symptoms:
 - Pain in extremities*
 - Back pain
 - Joint pain
 - Pain during urination
 - Other pain (excluding headaches)
- Cardiopulmonary symptoms:
 - Shortness of breath when not exerting oneself *
 - Palpitations
 - Chest pain
 - Dizziness
- Conversion/pseudoneurologic symptoms:
 - Amnesia*
 - Difficulty swallowing*
 - Loss of voice
 - Deafness
 - Double vision
 - Blurred vision
 - Blindness
 - Fainting or loss of consciousness
 - Seizure convulsion
 - Trouble walking
 - Paralysis or muscle weakness
 - Urinary retention or difficulty urinating
- Sexual symptoms (for the major part of the patient's life after the beginning of opportunities for sexual activity):
 - Burning sensation in sexual organs or rectum (other than during intercourse)*
 - Sexual indifference
 - Pain during intercourse
 - Impotence
- Female reproductive symptoms (judged by the patient to occur more frequently or severely than in most women):
 - Painful menstruation*
 - Irregular menstrual periods
 - Excessive menstrual bleeding
 - Vomiting throughout pregnancy

* These seven items may be used to screen for SD. The presence of two or more of these items suggests a high likelihood of the disorder.

acutely talented at detecting physician doubt as well. It may help the physician to keep in mind Wilder Penfield's maxim: "Assume the pain is real (that is, consciously experienced by the patient even if not a result of tissue damage) unless you

have incontrovertible proof that the patient is malingering."⁷ Certainly our current state of ignorance regarding mind-brain/body relationships justifies such a stance.

The primary care physician should have an objective medical reason for ordering consultation or expensive or invasive diagnostic tests for such patients. Such a management strategy reduces health care costs by about 50%.^{47,48}

In one study,⁴⁸ a single psychiatric consultation led to significantly reduced ordering of expensive diagnostic tests. Median quarterly total health care charges dropped from \$765 to \$158, and the annual number of days of hospitalization dropped from 6.4 to 2.4. However, outpatient visits did not decrease, because part of the recommended management protocol was scheduling regular visits at four- to six-week intervals.

The deliberate avoidance of hospitalizations, diagnostic procedures, and surgeries may evoke some malpractice anxiety for the primary care physician. Once the SD patient's condition is diagnosed, it must be remembered that more care is not necessarily better care. However, new symptoms need to be taken seriously for two reasons: (1) to reassure the patient and confirm the validity and seriousness of her suffering; and (2) to detect any objectively verifiable illness that might arise.

The use of psychotropic medications for SD patients requires more caution than usual. SD patients probably make up a significant proportion of iatrogenic substance abusers. They are prone to self-medicating and to misinterpreting the signs and symptoms of withdrawal from prescribed medications (for example, rebound insomnia following withdrawal of soporifics); thus, they remedicate themselves to cope with the absence of the regimen.

Repeated admonitions regarding the risks of developing a dependence or abuse disorder are helpful if such a development is presented as one of the frequent complications of being sickly. The fact that treatment sometimes can be worse than living with the illness should be emphasized. Low-dose, short-term prescription of psychotropic agents may, because of the placebo effect or the implicit social communication that "this is real sickness, because the doctor gave me medicine," also reassure the patient who is in a symptom-aggravating interpersonal crisis.

Insight-oriented/cognitive psychotherapy may be of assistance in enabling patients to attribute their physical symptoms to interpersonal and emotional causes, but it must be presented to the patient as an adjunct to medical care. Framing the patient's illness as stress-caused or aggravated, rather than

emotional or mental, sometimes can make counseling an acceptable therapy.^{47,49} In one study⁴⁷ of a short-term (six to 12 sessions) treatment program for Medicaid and Blue Cross abusers (patients who fell into the top 10% of medical charges with no verifiable illness), medical costs decreased by 47%.

The practitioner's primary goal with such patients should be prevention of iatrogenic harm. By providing a sympathetic ear and confirmation of the legitimacy and seriousness of the patient's suffering, the physician can avoid having the patient "doctor shop." Such physician-shopping eventually results in receipt of prescription drugs, drug abuse, or aggressive, expensive, and risky diagnostic procedures.^{29,48-52} Once this primary goal is accomplished, the task of gently suggesting the role of psychologic determinants can be undertaken.

Summary

Somatization disorder is characterized by a history of multiple somatic complaints that are unverified by objective evidence. These patients, typically female, are prone to doctor-shopping, prescription abuse, and multiple, expensive, and unnecessary workups. Once the diagnosis is made, SD patients are best managed by sympathetic primary care physicians who are conservative in their pursuit of medical explanations for the patient's complaints. Somatization disorder patients generally are resistant to psychologic explanations for their problems, but some will accept referral for counseling if it is presented as adjunctive to medical care and framed as treatment of "stress" rather than "emotional" or "mental" problems.

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From the Center for Behavioral Medicine, College of Osteopathic Medicine of Oklahoma State University, Tulsa.

Reprint requests to Dr Ketterer, Psychiatry, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202.