Minor tranquillizers in somatic disorders

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Conclusive evidence of improved outcome due to adjunctive anxiolytic therapy in some somatic conditions is lacking. However, such therapy may facilitate patient management without being "curative". The resulting improved feeling of well-being may be of value in the management of gastrointestinal disorders, migraine and myocardial infarction. Negative effects may be observed in acute respiratory conditions, especially during acute exacerbations of chronic conditions, with the administration of benzodiazepines; hence they should be used with caution. The use of these agents in treating persons with hypertension seems to be of no value and may even be detrimental. Careful evaluation of each case is desirable, and treatment should be planned with its termination in mind.

La preuve définitive d'une amélioration due à la thérapie anxiolytique adjointe dans certaines conditions somatiques manque toujours. Cependant de telle thérapie peut faciliter le traitement du patient sans toutefois effectuer une guérison complète. L'amélioration du sentiment de bien-être provoqué par ces agents peut s'avérer avantageuse dans le traitement de troubles gastrointestinaux, de migraine et d'infarctus du myocarde. Des effets nocifs peuvent être notés chez les patients souffrant de conditions respiratoires aiguës, surtout lors d'exacerbations aiguës de conditions chroniques, avec l'administration des benzodiazépines; leur utilisation doit donc se faire avec précaution. L'usage de ces agents chez les personnes souffrant d'hypertension ne semble aucunement justifiée et peut même s'avérer nuisible. L'évaluation attentive de chaque cas est hautement désirable, et le traitement devrait être planifié avec une fin en vue.

Anxiolytic drugs are among the most widely prescribed drugs in medicine. Most of the prescriptions for these agents are written not by psychiatrists but by general practitioners or other specialists. In fact, 97% of internists and general practitioners have at one time or another prescribed diazepam, a benzodiazepine derivative.[1] In 1972 two thirds of the 77 million benzodiazepine prescriptions in the United States were for diazepam and an additional 4 million were for flurazepam, a benzodiazepine hypnotic.[2]

A large proportion (one third to one fifth) of the patients seen in physicians' offices have emotional difficulties, and many of them have primary or psychogenic physical complaints.[3] Minor tranquillizers are often prescribed as adjunctive therapy in the treatment of many of the so-called psychosomatic disorders. Since physicians generally consider these disorders as physical dysfunctions in which psychic or emotional factors have an initiating role or contribute to the persistence of the disorder, and since physicians want "to treat", minor tranquillizers seem to have become a panacea for various "psychosomatic" disorders.

In this review we assess the value of adjunctive anxiolytic therapy in functional gastrointestinal disorders such as peptic ulcer and ulcerative colitis, migraine, asthma and other respiratory disorders, angina and myocardial infarction, and hypertension. Such an assessment is rendered difficult by the paucity of reports of pertinent controlled studies and by the lack of standardized objective criteria of improvement that may be attributable to anxiolytic therapy in such conditions.

Gastrointestinal disorders

Literature dated in the early 1960s claimed that diazepam could be used to treat gastric and duodenal ulcers, psychogenic epigastric disorders, irritable colon and intestinal spasms. In recent years, however, these claims have not been appearing in company information. One manufacturer says diazepam is recommended for use in, simply, "anxiety states with somatic expression".[4] This seems to indicate a possible tightening of the manufacturer's claims. The chlordiazepoxide–clidinium combination Librax is claimed to be useful in the adjunctive management of various gastrointestinal disorders;[5] the clidinium component may have a major effect on decreasing gastrointestinal secretions and motility because of its anticholinergic action.

A number of investigators have had "good results" in treating gastrointestinal disorders with minor tranquillizers. Deutsch[6] reported relief of anxiety in a double-blind study

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of patients treated for diagnosed functional gastrointestinal disorders; with diazepam–propantheline combinations the overall improvements in global ratings were significantly better than with placebo–propantheline combinations. Voegtlin[7] found that diazepam was an effective adjunct in the symptomatic management of diagnosed functional gastrointestinal disorders such as irritable colon syndrome and functional diarrhea with associated nervous tension and anxiety. Another study[8] demonstrated that the prevailing effect of diazepam treatment of gastrointestinal disorders was relaxation, with apparent alleviation of the "spasm–pain–increased spasm" cycle common in such patients.

The chlordiazepoxide–clidinium combination Librax is claimed to be effective in the treatment of peptic ulcers, gastritis, gastrointestinal hyperactivity or hypermotility, pylorospasm, duodenitis, colitis, irritable colon and other functional or organic disorders of the gastrointestinal tract.[4] Clidinium is an anticholinergic with antispasmodic and antisecretory activity. Brown[9] found that chlordiazepoxide gave "good results" in patients experiencing anxiety and functional gastrointestinal distress.

Other minor tranquillizers such as clorazepate dipotassium and lorazepam have been used by patients with moderate anxiety associated with gastrointestinal diseases, again with "good results"; Kasich[10] showed that clorazepate was superior to placebo but not significantly different from diazepam in overall anxiolytic effect. In a double-blind crossover study by Furtado[11] lorazepam was shown to be useful in the treatment of "gastrointestinal neurosis", and Kasich, Richards and Vanov[12] showed that lorazepam was comparable to diazepam as an adjunct in the management of chronic gastrointestinal disease with anxiety.

The Medical Letter[13] noted that "many clinicians prescribe sedatives, since chronic emotional stress is probably a contributing factor in the development of ulcers. For patients with severe pain, especially those with gastric ulcers, some *Medical Letter* consultants recommend bed rest. Its effectiveness may be due more to psychological than to physical factors."

In many of the studies reviewed, the criteria for "good results" were the patient's improved feeling of well-being and, in some cases, the investigator's evaluation based on global ratings. Other products and techniques such as anticholinergics, absorbents, roughage-free diets and small doses of codeine, diphenoxylate hydrochloride–atropine (Lomotil) and steroids by rectum were given concomitantly in many of the studies.[6,7,9,11,12] Although emotional factors are often associated with peptic ulcers and appear to precipitate recurrence, there is no evidence that they have a role in maintaining the chronic peptic ulcer once it has been reactivated.

Many of the antianxiety drugs, such as diazepam, reduce basal gastric secretion of acid. Roberts and Oldrey[14] found that in 10 male patients with dyspepsia intravenous administration of diazepam did not significantly suppress gastric secretion in the first hour after stimulation with pentagastrin, but once the "maximal" effect of pentagastrin had worn off gastric secretion was strongly suppressed. It was also found that diazepam had no effect on nocturnal basal (unstimulated) gastric secretion of acid, which suggested that diazepam acts by inhibiting the secretory stimulation that arises centrally, during wakefulness; this would make it a useful therapeutic aid when "stress" was a factor. Further to this, Stacher and Starker[15] found in studying the inhibitory effect of bromazepam on insulin-stimulated gastric acid secretion that sleep and drowsiness rather than bromazepam seemed to cause the inhibition. More recently Stacher and associates[16] suggested that lowered basal as well as insulin-stimulated gastric acid secretion after bromazepam administration was due to the central effect of the drug. It may therefore be more appropriate to prescribe a minor tranquillizer for use during the day and an effective anticholinergic for use at bedtime rather than a hypnotic for insomnia due to persistent nocturnal pain. If pain and insomnia persist, both may be needed.

In prescribing minor tranquillizers one should usually titrate the dose to counteract the episodic fluctuation of anxiety. Doses can be increased with increasing anxiety and reduced during remissions (or use of the drug can be stopped). Controlled studies have shown that these agents are helpful during short-term use but lose their demonstrable effectiveness with long-term use.[17,18] Consequently long-term use should be avoided. Since chlordiazepoxide and diazepam are long-acting and have pharmacologically active metabolites, more than one or two daily doses are rarely needed.[19] Potential accumulation may be decreased with this method of administration and full use made of the agent's short-term effect.

Although adjunctive therapy with minor tranquillizers is reported to be associated with an improvement in the patient's well-being and a decrease in symptoms it is not clear whether these patients have greater anxiety than the general population. Minor tranquillizers may alleviate acute concomitant anxiety in the short term, but other means of decreasing anxiety must be found to supplement the effectiveness of these drugs, which is known to wane. This would entail a good, supportive patient–physician relationship, familial support and adjustments in lifestyle. There are no experimental data to indicate that these drugs hasten recovery from gastrointestinal disorders. The endpoints for assessment are subjective and are blurred by the concomitant reduction in anxiety plus the frequently added feeling of well-being brought on by these drugs. The physical disease state may still be active but the emotional reaction is blunted. The use of these drugs should be based on consideration of the psychologic and symptomatic features of the illness rather than any effect on a pathologic process.

Migraine

Over 400 remedies have been proposed in the treatment of migraine,[20] some of which are psychotropic agents. These may be minor tranquillizers or antidepressants used in doses that are subtherapeutic for antidepressant activity but nevertheless sufficient to be sedative. The double-blind study of Okasha, Ghaleb and Sadek[21] in 80 patients suffering from migraine showed that doxepin, 10 mg three times daily, gave the best response, amitriptyline, 10 mg three times daily, was next most effective and diazepam, 2 mg

three times daily, had a weaker effect but was superior to placebo. Santos and Unger[22] reported satisfactory results in patients given hydroxyzine. Four patients were said to be maintained "quite free" of headaches, but this expression was not clearly defined in their report. Clorazepate dipotassium in combination with dihydroergotamine tartrate showed good therapeutic results, which were confirmed in a follow-up assessment, in 31 of 40 patients with migraine; in the remaining 9 patients migraine persisted but was less frequent.[19] Since an ergot derivative was used in combination with a minor tranquillizer, evaluation of the efficacy of the tranquillizer is difficult. Few reports are available of studies demonstrating the effectiveness of tranquillizers alone in the treatment of migraine. As a single treatment, ergot derivatives seem to be most effective for acute attacks.[20]

It has been suggested that headache or migraine may be relieved with use of an ice bag and bedrest in a dark room.[20,23] Working may make the headache worse and prolong it for days rather than hours. Diazepam or another sedative in small doses may be necessary for sleep, but the majority of migraine attacks seem to be helped within a few hours with analgesic–antiemetic combinations and occasionally a sedative.[23] Methysergide maleate seems to be the preferred drug for prophylaxis[20,24] but its use is limited by long-term side effects.[20] Pizotyline shows promise and may overtake methysergide in the near future.[25] Benzodiazepines may be of benefit in migraine prophylaxis by reducing anxiety and modifying reactions to frustration; small doses of antidepressants seem to be more effective in this condition, which suggests involvement of a mechanism of action that is yet to be defined.[24]

Asthma and other respiratory disorders

Minor tranquillizers have been used to reduce the anxiety component of asthma and various respiratory disorders. It has been suggested that hydroxyzine may be useful "as adjunctive therapy in . . . allergic conditions with strong emotional overlay, such as in asthma".[26] Hydroxyzine has been studied in combination with a variety of other forms of treatment.

In a double-blind study with 16 patients Blerman, Pierson and Shapiro[27] showed that ephedrine, 25 mg, had no effect on postexercise asthma, hydroxyzine, 10 mg, had a weak effect in hastening recovery and theophylline, 130 mg, modified the postexercise response significantly, while the three together produced an additive effect superior to that of theophylline alone. Santos and Unger[22] selected hydroxyzine to control allergic disorders with its ataractic and antihistaminic properties. Patients reported greater calmness and were able to rest and sleep better. In none did the disorder clear completely, but less antiasthmatic medication was claimed to be required, though the reduction was not clearly defined. Santos and Unger thus reported results that can be expected with the use of minor tranquillizers, which suggests that these drugs have a primarily adjunctive role in the treatment of asthma but no specific therapeutic action. In the same vein Spankus[8] found that three of five patients had "excellent results" with diazepam; however, the small numbers and the nonspecificity of the clinical criteria limit the conclusions that can be drawn.

An ephedrine–theophylline–hydroxyzine combination was compared with salbutamol by Alanko, Lahdensuo and Mattila[28] in 15 patients with asthma. Overall the combination was superior to salbutamol as judged from measurements of peak expiratory flow, severity of symptoms and number of isoproterenol inhalations needed per day. Similar results were obtained by Chodosh and Doraiswami:[29] when hydroxyzine was added to a theophylline–ephedrine regimen there was a greater improvement in the results of most pulmonary function tests than with theophylline–ephedrine alone.

Probably of greater consideration is not whether minor tranquillizers are efficacious in the treatment of respiratory diseases, but whether side effects limit their usefulness. Between asthma attacks, pulmonary function may be normal or nearly normal and the patient relatively free of symptoms. It is estimated that in about one third of persons with asthma, emotional strain and specific stressful situations may be important factors in the initiation of asthma attacks.[30] Sedatives may be required early in the acute phase to allay agitation and relieve anxiety,[30] but as the attack progresses the respiratory depressant effect of these drugs may contribute to serious problems in patient management.

Notwithstanding the possibility of acute asthma attacks in individuals hypersensitive to diazepam,[31] benzodiazepines have documented respiratory depressant effects in patients with and without pulmonary disease.[32-40] Such effects have been sought after intravenous or oral administration of diazepam, lorazepam, chlordiazepoxide and nitrazepam. Catchlove and Kafer[34] assessed diazepam treatment in patients with chronic obstructive pulmonary disease and asthma in acute exacerbation. They observed clinical deterioration following diazepam administration in some patients, accompanied by worsening of blood gas abnormalities out of proportion to the degree of obstruction. Clark, Collins and Tong[36] suggested that restlessness, which might be thought to be an indication for sedation, may actually be a sign of worsening respiratory failure. Hence sedation would be contraindicated.

Kronenberg and colleagues[38] administered diazepam, 10 mg four times daily for 5 days, to six patients with severe but stable obstructive pulmonary disease and hypercapnea. No significant changes in the forced expiratory volume in 1 second or in arterial blood tensions occurred. Three patients continued to take the drug (5 to 15 mg daily) for 15 to 25 months with no adverse effects. In this study diazepam was administered orally and the patients' conditions were stable. The study by Zsigmond, Shively and Flynn[41] of patients with stable chronic obstructive pulmonary disease undergoing treatment demonstrated the safety of doses of 0.15 mg/kg of diazepam administered intravenously.[41] These doses caused no ventilatory depression in patients with severe disease. This finding differs from that of Catchlove and Kafer,[34] who dealt with patients during their recovery from an acute exacerbation, which may explain the seemingly contradictory results.

A bronchodilating effect apparently accompanies parenteral adminis-

tration of 50 to 100 mg of hydroxyzine; hence this drug has been suggested for the treatment of asthma.[29] More controlled studies are required for better evaluation of its therapeutic value.

The emotional factors so frequently present in patients with asthma often necessitate the use of sedatives and tranquillizers. However, because all sedatives have some degree of respiratory depression, the need for their use during acute episodes should be carefully determined. The agitation, confusion and irritability observed during exacerbations of asthma may be the result of hypoxemia or hypercapnia or both. When these abnormalities are present the use of any sedative may lead to depression of the respiratory centre, thus aggravating the pre-existing impairment of air exchange.[42] The magnitude of the depressive effects is of uncertain clinical significance,[43] so until evidence is conclusive, no sedative can be considered safe.

Although some of the psychotropic drugs have provided some subjective relief, none has been demonstrated to have a lasting effect on asthmatic dysfunction.[44]

Angina and myocardial infarction

Sedatives and anxiolytic agents are often prescribed to facilitate the management of a patient with angina or myocardial infarction. The physical and emotional stresses that may precipitate chest pain must be identified and an attempt made to adjust the patient's lifestyle as well as his reaction to these stresses. In acute myocardial infarction sedation is important during hospitalization, when 24-hour surveillance and forced inactivity may contribute to the patient's frustration.

Melsom and associates[45] studied 38 patients hospitalized with proven myocardial infarctions. Half of the patients received 10 mg of diazepam intravenously immediately and 15 mg orally 1 hour later and every 8 hours thereafter for 3 days. The other 19 patients served as controls. It seemed that patients in the diazepam group were safely and pleasantly sedated and had less need for analgesics. They also had reduced urinary excretion of catecholamines. It was proposed that diazepam decreased stress reactions, which in turn reduced the frequency of serious arrhythmias and prevented the existing myocardial injury from spreading.

Similar results were obtained by Gedeon and Varkonyi[46] in 22 patients with agitation associated with acute myocardial infarction: they responded well to 10 mg of diazepam given intravenously and fell into a deep, calm, atonic sleep. The pulse rates decreased and the pulse amplitude increased. No effect on respiration or circulation was noted. Intramuscular injection of the same dose did not produce comparable results and restlessness was not markedly changed; it was suggested that adequate blood concentrations may not be obtained with intramuscular administration. Kanto's[47] study also demonstrated that intravenous or oral administration of diazepam was superior to intramuscular injection.

Hackett and Cassem[48] showed that chlordiazepoxide, 10 mg, and amobarbital, 50 mg, were equally effective as anxiolytic agents in a double-blind randomized study of 58 patients in a coronary care unit. They found that patients receiving chlordiazepoxide had fewer side effects, required narcotic and hypnotic medications less often, and remained in intensive care for shorter periods.

There is no evidence that minor tranquillizers reduce the frequency of anginal attacks, but anxiolytic drugs may be important in relieving the stress and anxiety brought on by angina and myocardial infarction. This does not preclude the other sound principles of medical management. Benzodiazepines offer certain advantages over barbiturates in not interfering with the action of coumarins.[49] Moreover, diazepam administered intravenously does not seem to have appreciable adverse hemodynamic effects in patients with impaired cardiac function.[50,51]

Hypertension

Abel and Reis[50] noted that diazepam, 0.1 mg/kg, administered intravenously to patients after cardiac operations cause a small but significant decrease in both systolic and diastolic blood pressure, along with a simultaneous increase in stroke volume. Improvements in cardiac function and decreases of 7 to 8 mm Hg in mean aortic pressure with doses of 0.1 mg/kg of diazepam were found in a study by Côté, Guéret and Bourassa.[51] It was suggested that, in addition to central sedative effects, the drug had a nitroglycerin-like action on the coronary and systemic circulation. Decreases in systolic and diastolic blood pressure have been noted following intravenous administration of diazepam and subsequent cardioversion.[52]

Most of the studies available have dealt with the pharmacologic effects of diazepam or other benzodiazepines in man[51,52] and in animals,[53,54] intravenous administration producing modest decreases in blood pressure during brief surgical procedures. We could find no reports discussing the continuing oral use of these agents as adjuncts in the treatment of hypertension. The effect of intravenous administration in dogs was transitory, lasting for 5 to 10 minutes and up to 1 hour with larger doses,[54] and eventual tolerance to long-term administration of minor tranquillizers could limit their effectiveness in the treatment of hypertension.

Greenblatt, Shader and Lofgren[43] discussed the "unfortunate" practice of prescribing anxiolytic drugs rather than specific antihypertensive agents for persons with hypertension. Anxiolytic agents have no specific hypotensive effects, and if the blood pressure is lowered it is the result of central nervous system depression. Consequently, one is left with a drowsy and still hypertensive patient.

Benzodiazepines may be useful in the treatment of hypertension because of their role in the control of anxiety mediated by the central nervous system and because of their direct effect on the cardiovascular system,[54] but not enough data are available for evaluation. Anxiolytics may be useful as adjuncts to antihypertensive medication, but only if anxiety seems to contribute to increased blood pressure, and this is difficult to demonstrate clinically; hence such use of these agents is probably without value. *The Medical Letter*[55] has stated: "Diazepam is not an antihypertensive drug and it has not been shown to be useful in the long-term treatment of hypertension. Furthermore, there is no evidence that diazepam enhances the antihypertensive effect of any blood pressure reducing drug".

Conclusions

Minor tranquillizers have been and are being used to treat a wide variety of somatic disorders. Conclusive evidence of improved outcome due to anxiolytic effects is lacking. However, the role of these agents is adjunctive — that is, it may facilitate patient management and improve the state of well-being without being "curative". Most of the data available to assess the value of this adjunctive treatment are anecdotal and not amenable to comparative analysis. However, for certain conditions there are studies that indicate a rationale for the use of these agents; acute myocardial infarction is one condition in which the use of benzodiazepines is probably beneficial. On the other hand, in acute respiratory conditions, especially during acute exacerbations of chronic conditions, negative therapeutic effects may result from the use of benzodiazepines. In migraine and gastrointestinal disorders the anxiolytic properties of benzodiazepines may contribute to a decrease in the self-perpetuating cycle of pain–anxiety–pain. In this way these drugs may be considered as adjuncts in treatment. This rationale has to be considered theoretical and not an automatic justification of anxiolytic administration.

It is important for the clinician to assess the role of psychologic factors in the illness being treated and to judge carefully whether adjunctive treatment with anxiolytics is necessary. The drawbacks of initiating this form of treatment must be considered in each case. In general, treatment should be planned with its termination in mind.

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References

1. WINSTEAD DK, LAWSON T, ABBOTT D: Diazepam use in military sick call. *Milit Med* 141: 180, 1976
2. GREENBLATT DJ, SHADER RI: Drug therapy: benzodiazepines (first of two parts). *N Engl J Med* 291: 1011, 1974
3. BLACKWELL B: Psychotropic drugs in use today: the role of diazepam in medical practice. *JAMA* 225: 1637, 1973
4. *Valium,* product information, Montreal, Hoffmann-La Roche
5. *Librax,* product information, Montreal, Hoffmann-La Roche
6. DEUTSCH E: Relief of anxiety and related emotions in patients with gastrointestinal disorders. *Am J Dig Dis* 16: 1091, 1971
7. VOEGTLIN WL: Management of functional gastrointestinal disorders with diazepam. *Appl Ther* 6: 801, 1964
8. SPANKUS WH: Role of a new psychotropic drug in somatic disorders. *Psychosomatics* 5: 153, 1964
9. BROWN CH: Clinical evaluation of Librium in gastrointestinal diseases. *Am J Gastroenterol* 35: 30, 1961
10. KASICH AM: Clorazepate dipotassium in the treatment of anxiety associated with chronic gastrointestinal disease. *Curr Ther Res* 15: 83, 1973
11. FURTADO JD: Lorazepam in gastrointestinal disorders with anxiety overlay. *Psychosomatics* 17: 32, 1976
12. KASICH AM, RICHARDS DJ, VANOV SK: Lorazepam in management of anxiety associated with chronic gastrointestinal disease: a double-blind study. *Curr Ther Res* 19: 292, 1976
13. Medical treatment of peptic ulcer. *Med Lett Drugs Ther* 11: 105, 1969
14. ROBERTS DM, OLDREY TBN: The effect of diazepam on pentagastrin-stimulated and nocturnal (sleeping) gastric secretion in man. *Am J Gastroenterol* 63: 396, 1975
15. STACHER G, STARKER D: Inhibitory effect of bromazepam on insulin-stimulated gastric acid secretion in man. *Am J Dig Dis* 20: 156, 1975
16. STACHER G, BAUER P, BRUNNER H, et al: Gastric acid secretion, serum-gastrin levels and psychomotor function under the influence of placebo, insulin-hypoglycemia, and/or bromazepam. *Int J Clin Pharmacol Biopharm* 13: 1, 1976
17. SWANSON DA: Benzodiazepines in psychiatry. *S Afr Med J* 49: 1829, 1975
18. KELLETT JM: The benzodiazepine bonanza (C). *Lancet* 2: 964, 1974
19. SKUPIN G, FRANZKE HG: Di Stellung von Dikalium-chlorazepat (Tranxilium) in der Therapie psychovegetiver Syndrome. *Med Klin* 70: 1279, 1975
20. PARKES JD: Diseases of the central nervous system. Relief of pain: headache, facial neuralgia, migraine, and phantom limb. *Br Med J* 4: 90, 1975
21. OKASHA A, GHALEB MH, SADEK A: A double blind trial for the clinical management of psychogenic headache. *Br J Psychiatry* 122: 181, 1973
22. SANTOS IMH, UNGER L: Hydroxyzine (Atarax) in allergic diseases. *Ann Allergy* 18: 172, 1960
23. The treatment of acute migraine attacks (E). *Headache* 15: 291, 1976
24. BANKS S, SAUNDERS SJ, MARKS IN, et al: Gastrointestinal and hepatic diseases, in *Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics,* AVERY GS (ed), Littleton, Publishing Sci, 1976, p 782
25. SPEIGHT TM, AVERY GS: Pizotifen (BC 105): a review of its pharmacological properties and its therapeutic efficacy in vascular headaches. *Drugs* 3: 159, 1972
26. ROTENBERG GN, OTTERBEIN NL, HUGHES FN (eds): *Compendium of Pharmaceuticals and Specialties,* 12th ed, Toronto, Can Pharm Assoc, 1977, p 62
27. BLERMAN CW, PIERSON WE, SHAPIRO GG: The pharmacological assessment of single drugs and drug combinations in exercise-induced asthma. *Pediatrics* 56 (suppl): 919, 1975
28. ALANKO K, LAHDENSUO A, MATTILA MJ: Bronchodilator effect of oral salbutamol and an ephedrine + theophylline + hydroxyzine combination in asthmatic out-patients. *Scand J Respir Dis* 55: 340, 1974
29. CHODOSH S, DORAISWAMI S: An evaluation of theophylline–ephedrine with and without hydroxyzine in asthma. *Curr Ther Res* 18: 773, 1975
30. NORMAN PS: Asthma, hay fever, and other manifestations of allergy, in *Harrison's Principles of Internal Medicine,* 7th ed, WINTROBE M, THORN GW, ADAMS RD, et al (eds), New York, McGraw, 1974, p 371
31. BLUMBERG MZ, YOUNG S: Diazepam-associated asthma. *Pediatrics* 54: 811, 1974
32. RAO S, SHERBANIUK RW, PRASAD K, et al: Cardiopulmonary effects of diazepam. *Clin Pharmacol Ther* 14: 182, 1973
33. DENAUT M, YERNAULT JC, DE COSTER A: Double-blind comparison of the respiratory effects of parenteral lorazepam and diazepam in patients with chronic obstructive lung diseases. *Curr Med Res Opin* 2: 611, 1975
34. CATCHLOVE RFH, KAFER ER: The effects of diazepam on respiration in patients with obstructive pulmonary disease. *Anaesthesiology* 34: 14, 1971
35. MODEL DG: Nitrazepam induced respiratory depression in chronic obstructive lung disease. *Br J Dis Chest* 67: 128, 1973
36. CLARK TJH, COLLINS JV, TONG D: Respiratory depression caused by nitrazepam in patients with respiratory failure. *Lancet* 2: 737, 1971
37. MODEL DG, BERRY DJ: Effects of chlordiazepoxide in respiratory failure due to chronic bronchitis. *Lancet* 2: 869, 1974
38. KRONENBERG RS, COSIO MG, STEVENSON JE, et al: The use of oral diazepam in patients with obstructive lung disease and hypercapnia (C). *Ann Intern Med* 83: 83, 1975
39. HUCH R, HUCH A: Respiratory depression after tranquillizers. *Lancet* 2: 1267, 1974

40. GRICE AS: SIDS — is this the answer? (C). *Med J Aust* 2: 809, 1975

41. ZSIGMOND EK, SHIVELY JG, FLYNN K: Diazepam and meperidine on arterial blood gases in patients with chronic obstructive pulmonary disease. *J Clin Pharmacol* 15: 464, 1975

42. BOCCLES JS: Problems of hydration, expectorants, antihistamines and sedatives in asthma, in *Bronchial Asthma: Mechanisms and Therapeutics,* WEISS EB, SEGAL MS (eds), Waltham, Mass, Little, 1976, p 802

43. GREENBLATT DJ, SHADER RI, LOFGREN S: Rational psycho-pharmacology for patients with medical diseases. *Annu Rev Med* 27: 407, 1976

44. KNAPP RH, MATHE AA, VACHON L: Psychosomatic aspects of bronchial asthma, in *Bronchial Asthma: Mechanisms and Therapeutics,* op cit, p 1070

45. MELSOM M, ANDREASSEN P, MELSOM H, et al: Diazepam in acute myocardial infarction. Clinical effects and effects on catecholamines, free fatty acids, and cortisol. *Br Heart J* 38: 804, 1976

46. GEDEON A, VARKONYI S: Symptomatic treatment of myocardial infarction and acute psychosyndrome with Seduxen injections. *Ther Hung* 21: 41, 1973

47. KANTO J: Plasma concentrations of diazepam and its metabolites after peroral, intramuscular, and rectal administration — correlation between plasma concentration and sedatory effect of diazepam. *Int J Clin Pharmacol Biopharm* 12: 427, 1975

48. HACKETT TP, CASSEM NH: Reduction of anxiety in the coronary-care unit: a controlled double-blind comparison of chlordiazepoxide and amobarbital. *Curr Ther Res* 14: 649, 1972

49. *Evaluations of Drug Interactions,* 2nd ed, Washington, Am Pharm Assoc, 1976, p 276

50. ABEL RM, REIS RL: Intravenous diazepam for sedation following cardiac operations: clinical and hemodynamic assessments. *Anesth Analg (Cleve)* 50: 244, 1971

51. CÔTÉ P, GUÉRET P, BOURASSA MG: Systemic and coronary hemodynamic effects of diazepam in patients with normal and diseased coronary arteries. *Circulation* 50: 1210, 1974

52. FORSSELL G, NORLANDER R, NYQUIST O, et al: Diazepam in cardioversion. *Acta Med Scand* 197: 255, 1975

53. MERLO L, NOSEDA V, FERRINI R, et al: Effect of Camazepam (SB-5833), a new antianxious drug, on cardiac contractility and coronary hemodynamics. *Arzneim Forsch* 24: 1759, 1974

54. DANIELL HB: Cardiovascular effects of diazepam and chlordiazepoxide. *Eur J Pharmacol* 32: 58, 1975

55. Diazepam (Valium) in hypertension. *Med Lett Drugs Ther* 16: 96, 1974