# Barbiturate-Related Connective Tissue Disorders

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• **Development of Dupuytren's contractures, frozen shoulder, Ledderhose's syndrome, Peyronie's disease, fibromas, and general joint pain has been linked in retrospective studies and case reports to the use of antiepileptic drugs. We undertook a prospective survey of the incidence of connective tissue disorders in 622 patients newly treated with carbamazepine, phenobarbital, phenytoin sodium, or primidone. Ten of the 406 patients who were treated for 6 months or more developed connective tissue disorders. All affected patients were taking a barbiturate (primidone, 4 patients; phenobarbital, 6 patients). Seven of the 10 problems occurred during the first year of treatment. These data are prospective evidence of a statistically significant relationship between barbiturate use and the development of connective tissue disorders, and timing of appearance.**

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In 1925, Maillard and Renard[1] called attention to an association between use of barbiturates and the appearance of localized and generalized joint pains. Several years later, Beriel and Barbier[2] noted similar stiffening of joints in upper and lower extremities, particularly the shoulders, of patients who were being treated with phenobarbital (Gardenal). They termed this disorder *rhumatisme gardenalique*. In subsequent years, periodic references were made to a variety of connective tissue disorders associated with use of antiepileptic drugs, mostly barbiturates. These included frozen shoulder,[2] Dupuytren's contractures with palmar nodules,[8] plantar fibromas or Ledderhose's syndrome,[4] heel and knuckle pads, Peyronie's disease,[5] and generalized aches and pain.[2,3]

Because such rheumatologic disorders are quite common in the general population, a causal relationship between these disorders and antiepileptic drugs has been probable but not certain. To our knowledge, there have been no prospective, controlled trials to demonstrate a selective increase of these problems in association with barbiturate use. The Veterans Administration Epilepsy Cooperative Study enrolled patients for initial treatment with a single antiepileptic drug.[6] This design allowed the first opportunity to observe prospectively whether use of specific antiepileptic drugs was associated with onset of any of these connective tissue disorders and to determine when problems were likely to appear.

## PATIENTS AND METHODS

Patients at 10 Veterans Administration medical centers (Augusta, Ga; Boston, Mass; Dallas, Tex; Durham, NC; Los Angeles, Calif; Minneapolis, Minn; San Diego, Calif; Sepulveda, Calif; Seattle, Wash; and West Haven, Conn) were entered into the Veterans Administration Epilepsy Cooperative Study from 1978 to 1983 and were followed up until the antiepileptic drug being administered failed to control seizures and caused excessive adverse effects, or until the patient left for non–drug-related reasons. Follow-up, which ranged from 1 to 6 years, was discontinued in 1984. The 622 patients included in the study were diagnosed as having localization-related (partial or symptomatic) epilepsy. More than half of the patients were newly diagnosed and had never been treated with an antiepileptic drug; 21% had taken a medication at some time in the past; and, at the time of entry, the remaining 21% were receiving medication at insufficient dosage to yield therapeutic serum concentrations. The double-blind prospective assessment used a protocol that has been reported in detail.[6,8] Screening excluded alcoholics, patients with insulin-dependent diabetes, patients taking isoniazid, and patients with progressive or unstable medical disorders. Patients were randomized to therapy with a single antiepileptic drug (either carbamazepine, phenobarbital, phenytoin sodium, or primidone) and a placebo used to mask drug identity. The mean age of this largely (87%) male population was 41 years (range, 18 to 70 years). Study design included directions to establish a dosage that provided serum concentrations in the mid to high therapeutic range, unless prevented by side effects. Seizure-free patients were also maintained in this therapeutic range.

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Throughout the study, drug serum concentrations were determined and hematologic and serum chemistry tests were performed at every follow-up visit.

Direct questions about specific problems such as Dupuytren's contracture, frozen shoulder, and Peyronie's disease were not asked. However, questions concerning general rheumatologic and orthopedic problems were addressed on history and during the examination. Evidence of disorders such as rheumatoid or lupus arthritis constituted cause for exclusion from the study. Using rating scales,[7] seizure frequency and the type and severity of typical antiepileptic drug side effects were recorded at every follow-up visit. Because joint pain was not anticipated as a common drug-related event, the chart of every patient already entered into the study was reviewed midway through the study, when this issue was recognized. Patients were interviewed and examined at 12 and 24 months to ascertain whether joint pain, stiff hands, contractures, or any connective tissue disorder was present. A review of concurrent and past medications was accompanied by patient interviews that were performed by an investigator who did not know which drug the patient was taking. A prestudy survey showed that none of the group of investigators was aware of the reported barbiturate relationship. It was possible to document the presence of joint pain prior to entry into the study for many patients, particularly those who continued to use nonsteroidal anti-inflammatory drugs during the study. Patients who started use of an anti-inflammatory drug during the study or sought a consultation for joint pain or contracture were questioned about the specific problem leading to the use of the adjunct medication or to the medical assessment. Investigators were able to define onset of connective tissue disorders during the course of the study by separating continuation and exacerbation of preexisting problems that occurred during the study from those that were truly of new onset.

## RESULTS

Ten male patients developed a connective tissue disorder during treatment with a single antiepileptic drug: 8, during the course of the study; and 2, shortly after completion of the study while they were still taking the medication. None of these 10 patients had been using an antiepileptic drug prior to the study. Patient 1 had been taking carbamazepine for 2 months before developing a transient skin rash and changing to primidone; frozen shoulder began 8 months later. Patient 4 received phenytoin therapy for 2 years in the first phase of the study; it was stopped because of diffuse peripheral polyneuropathy. Subsequently, the neuropathic symptoms improved. Alternate primidone treatment was given for the next 9 months. At that time, patient 4 developed stiff shoulders and hands as well as generalized arthralgias. The symptoms cleared after the patient's medication was changed to carbamazepine. Three patients had previously used alcohol in excess, but not in the year preceding entry into the trial. One patient had mild diabetes, which was controlled by diet. The frequency of prior alcohol use and diabetes mellitus was the same for patients taking barbiturates or carbamazepine and phenytoin. The mean age of the patients who developed connective tissue problems was 57 years, which was older than the mean age of the other patients in the study (41 years). Nonetheless, the average age of all patients given phenobarbital or primidone did not differ from that of the patients who were receiving carbamazepine or phenytoin. The mean drug serum concentrations at 6 months did not differ between the affected patients and the whole group (phenobarbital, 92 μmol/L affected and 101 μmol/L unaffected; primidone, 64 and 52 μmol/L; and derived phenobarbital, 72 and 66 μmol/L).

The Table shows the distribution of disorders that occurred in 10 of the 622 patients who started the study. Dupuytren's contractures, frozen shoulder, Peyronie's disease, and/or other symptoms of joint pain developed in 6 of 86 patients who took phenobarbital and in 4 of 92 patients who took primidone for 6 months or more. None of the 107 patients who were receiving carbamazepine and none of the 121 patients who were receiving phenytoin for six months or longer had new-onset connective tissue problems other than gum hypertrophy or idiosyncratic acute sensitivity. Overall, using $\chi^2$ analysis, it was found that 10 (6%) of 178 patients treated with a single barbiturate as the only antiepileptic therapy for 6 months or longer developed a connective tissue disorder within the mean 3-year follow-up period. This was significantly different from findings in the 228 patients receiving other drugs ($P<.001$).

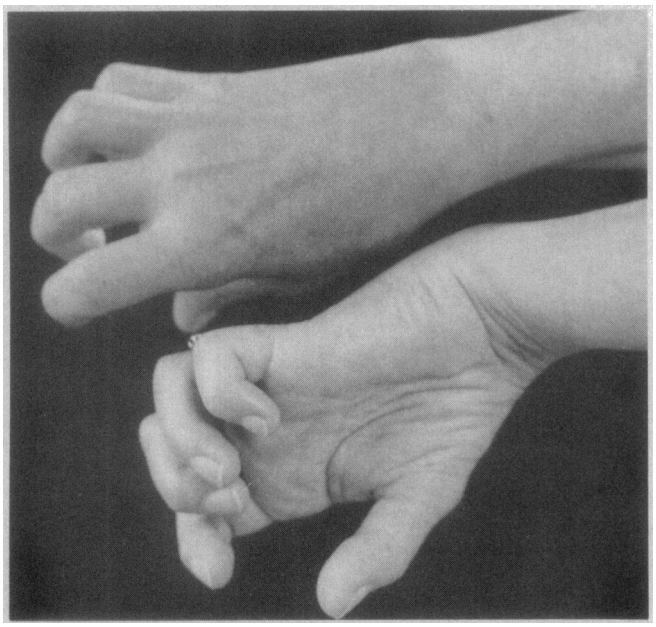
**Distribution of Disorders That Developed in 10 of 622 Patients During Monotherapy**

| Patient No./ Age, y | Disorder | Drug | No. of Months to Onset |
|---|---|---|---|
| 1/51 | Frozen shoulder, bilateral | Primidone | 8 |
| 2/43 | Frozen shoulder, left | Primidone | 28* |
| 3/67 | Shoulder pain, left | Phenobarbital | 4 |
| 4/67 | Arthralgias, bilateral | Primidone | 9 |
| 5/55 | Dupuytren's contractures, hands | Primidone | 6 |
| 6/45 | Dupuytren's contractures, hands | Phenobarbital | 3 |
| 7/70 | Dupuytren's contractures, hands | Phenobarbital | 22* |
| 8/56 | Dupuytren's contractures, toe | Phenobarbital | 6 |
| 9/7 | Peyronie's disease | Phenobarbital | 10 |
| 10/67 | Peyronie's disease and Dupuytren's contractures, hands | Phenobarbital | 24* |

*Diagnosed after completion of study.

One of the four patients (No. 5) who had developed Dupuytren's contractures improved during short-term follow-up when his medication was changed to carbamazepine. This patient was a typewriter repairman who readily noticed an increasing difficulty in using his hands while he was taking phenobarbital. Assuming that the problem was caused by arthritis, the patient was offered surgical treatment, which he declined because of his occupation. Instead, his antiepileptic drug was changed to carbamazepine, and improvement was noted without surgical repair. Another patient (No. 6) with Dupuytren's contractures was given indomethacin, with some relief of symptoms, and his medication was changed from phenobarbital to carbamazepine. A patient who reported arthralgia (No. 4) of the hands and left shoulder also improved when phenobarbital therapy was discontinued. The toe contracture in patient 8 resolved after phenobarbital therapy was discontinued. In all 10 patients who developed a connective tissue disorder, the complete blood cell count, erythrocyte sedimentation rate, and antinuclear antibody and rheumatoid factor tests were normal and there was no evidence of an inflammatory rheumatologic disorder.

Subsequent to study completion, a search was made for connective tissue disorders in nonstudy seizure patients seen at Yale Medical Center (New Haven, Conn) by one investigator (R.H.M.). Three women and two men were found whose connective tissue disorders also were associated with phenobarbital treatment. A 42-year-old woman developed fibrotic nodules and symptoms of aching joints, which improved when phenobarbital therapy was discontinued. A 55-year-old man with frozen shoulder and palmar nodules reported improve-



Bilateral finger flexion contractures in a 54-year-old woman taking phenobarbital.

ment with physical therapy after his drug was changed. Another patient (a 36-year-old woman) with chronic joint pain that was refractory to the usual therapy had complete relief of symptoms after her medication was changed from phenobarbital to carbamazepine. Severe disability occurred in a 54-year-old woman who had been taking phenobarbital along with other antiepileptic drugs for decades. She exhibited bilateral fixed finger flexion (Figure) and then developed a frozen knee joint after cast removal for a leg fracture. Roentgenograms of her joints showed no abnormalities. After her treatment was changed to valproate sodium monotherapy, her knee joint gradually loosened without any other specific therapy after being unmovable for 7 years.

## COMMENT

The results of this prospective controlled study demonstrated a statistically significant association between the use of barbiturates and connective tissue disorders (6% incidence) in male patients with epilepsy who had been receiving phenobarbital or primidone for at least 6 months. Development of these musculoskeletal problems in 7 of 10 patients during the first year of treatment suggests that the effect does not require decades of treatment but can occur during short-term use; it also implies that there is specific drug action rather than a general antiepileptic drug effect.

These results support the evidence documented in previous retrospective studies. Following the initial report in 1925 by Maillard and Renard,[1] the link between generalized connective tissue disorders and barbiturate use was noted by a number of other investigators. Lund[3] and, later, Critchley et al[9] noted the much higher incidence of these disorders (particularly Dupuytren's contractures) in patients with epilepsy in the 1940s than was reported by Fere and Francillon[10] at the turn of the century. The greatly increased number of reports of contractures suggested that a new syndrome had developed at about the time of the introduction of phenobarbital.[2] The frequent occurrence of shoulder-hand syndrome (frozen shoulder) was emphasized by Van der Korst et al.[11] Janz and Piltz[12] found that the association was even greater in patients who had been treated with primidone.

Connective tissue disorders are common in the adult population, with increasing incidence during aging,[18] as was true in the patients we describe. Several conditions are known to have a greater association with these disorders, including alcoholism and diabetes mellitus. Our patients were carefully screened to exclude those with evidence of alcohol abuse and were typical of an American outpatient clinic population in their current alcohol consumption. One of the five patients with Dupuytren's contractures (a 70-year-old man) had a history of alcoholism but had not used alcohol for 3 years prior to the study. One patient (No. 10) had non–insulin-dependent diabetes. The presence of these risk factors in the 622 patients we studied was equally frequent in those given barbiturates and those receiving carbamazepine or phenytoin.

The prevalence of connective tissue disorders in patients with epilepsy is not well established. Prior surveys have been retrospective and depended largely on cases involving patients who were referred for treatment. In addition, many patients described in previous studies were receiving more than one antiepileptic drug, making it difficult to be sure of the responsible agent. Critchley et al[9] emphasized the specific role of barbiturates. Fifty-six percent of 361 chronic epilepsy patients had some features of Dupuytren's contractures. All were receiving a barbiturate alone or in combination with other drugs. None of the 19 patients who were not being treated with a barbiturate had contractures.[9]

In this prospective study, we assessed all patients in whom therapy with a single antiepileptic drug had been started, and each patient was examined at 12 and 24 months for signs and symptoms of connective tissue disorders. A drawback to our study was the moderate length of follow-up, averaging 3 years. Late-onset cases may have occurred, but, with the exception of the two cases in West Haven, Conn, no data are available from other centers. Similar to the 6% incidence found in our outpatient population treated with barbiturates for at least 6 months, Froscher and Hoffmann[14] found that 5% of patients in a general epilepsy outpatient clinic population had contractures but that 20% of a subgroup of long-term patients with intractable seizures had such disorders. Six percent of the 267 outpatients evaluated by Janz and Piltz[12] had frozen shoulder while taking primidone. In contrast, Noble[15] indicated that his examination of institutionalized patients with epilepsy who had been receiving long-term treatment revealed an incidence of Dupuytren's contractures ranging from 10% to 38%. In the study of Critchley et al,[9] the duration of epilepsy and antiepileptic drug treatment was significantly associated with the presence of contractures ($P<.01$): more than half of the men treated for 20 years and the women treated for 30 years with a barbiturate developed contractures.[9] Thus, duration and dosage of barbiturate therapy play an important role in the development of connective tissue disorders.[9,11,16]

Looking at the issue from the viewpoint of the diagnosis, Horton and Gerster[17] noted that 17% of 149 patients with shoulder-hand syndrome were being treated with barbiturates. Van der Korst et al[11] also noted that 25 of 75 patients with shoulder-hand syndrome were receiving phenobarbital. This frequency is much higher than use of such drugs in the general population. These data showed a considerable increase in occurrence, incidence, and prevalence of connective tissue disorders in patients treated with phenobarbital compared to other drugs or other diseases.

Bilateral barbiturate-related disease was more common than were unilateral problems, usually by a ratio of 2:1.[11,16,17] Left-sided complaints were twice as common in patients seen by Critchley et al.[9] These problems are more common in male patients than in female patients, with reports of ratios ranging from 2:1[18] to 7:1.[13] Genetic factors have been considered in Dupuytren's contractures, which are familial in 10% of cases

in the general population.[18] Critchley et al[9] found no significant association between the pathogenesis of epilepsy and the presence of connective tissue disorders. They also found no association with the frequency or severity of seizures, thereby negating any possible disease contribution.

The mechanism of these connective tissue disorders is poorly understood. Dupuytren's contracture develops with a proliferation of elastic fibers and thickening of palmar collagen fiber bundles. These polyfibromatoses are due to a benign process of a "reweaving of the normal collagen architecture into a much tighter format," as described by Noble.[15] Pojer et al[19] considered this to be a "reparative hyperplastic growth of connective tissue." It is not well understood whether these disease states or the presence of chemicals such as alcohol, glucose, drugs, or metabolites causes the tissue changes. Isoniazid-induced shoulder-hand syndrome differs from barbiturate-induced disorders in that the onset of generalized joint pain and neuropathy is rapid, usually occurring within a month after therapy is started.[20] Janz and Piltz[12] indicated that primidone use causes frozen shoulder to begin slowly after 5 months to 15 years (mean, 4 years) of treatment, with a duration of 3 to 14 months (mean, 9 months).

Various surveys have found no link between hepatic enzyme activity and development of connective tissue disorders, despite a common pattern of enhanced activity during use of antiepileptic drugs and alcohol.[9,19] On the other hand, isoniazid probably inhibits some enzyme activity. Hurst et al[21] postulated that antiepileptic drug therapy caused decreased prostaglandin E, which in turn might allow palmar myofibroblasts contraction and lead to Dupuytren's contracture.

Several reports have indicated that the disease process reverses whether or not barbiturate therapy is discontinued but that much improvement is seen when the treatment is stopped.[3,13,16,17,21] Blanquart et al[17] noted that 11 of 16 patients improved within 1 to 4 months after phenobarbital therapy was discontinued, and the others improved later. Nevertheless, there was some spontaneous improvement observed while phenobarbital therapy was maintained. Similarly, continued treatment with phenobarbital did not hinder recovery from frozen shoulder in the three cases reported by Lequesne.[20] Janz and Piltz[12] also noted that there was reversibility of frozen shoulder whether or not primidone therapy was discontinued. Horton and Gerster[16] reported that optimum recovery was achieved only if the barbiturate treatment was stopped.

In conclusion, we have found that approximately 6% of patients treated for at least 6 months with phenobarbital or primidone developed a connective tissue disorder, most within the first year. This was significantly different ($P<.001$) from the incidence in patients receiving carbamazepine or phenytoin. The findings of this controlled trial indicate the importance of early investigation of problems reported by patients who are taking barbiturates. Transition to therapy with an alternate antiepileptic drug such as carbamazepine, phenytoin, or valproic acid may be advisable.

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## References

1. Maillard G, Renard G. Un nouveau traitement de l'epilepsie. *Presse Med.* 1925;20:1-4.

2. Beriel L, Barbier J. Le rhumatisme gardenalique. *Presse Med.* 1934;42:67-69.

3. Lund M. Dupuytren's contracture and epilepsy. *Acta Psychiatr Neurol.* 1941;16:465-492.

4. Schmidt D, Beck-Mannagetta G, Sorensen H. Plantar fibroma associated with phenobarbital treatment. In: Oxley J, Janz D, Meinardi H, eds. *Chronic Toxicity of Antiepileptic Drugs.* New York, NY: Raven Press; 1983:133-145.

5. Schmidt D. Connective tissue disorders induced by antiepileptic drugs. In: Oxley J, Janz D, Meinardi H, eds. *Chronic Toxicity of Antiepileptic Drugs.* New York, NY: Raven Press; 1983:115-124.

6. Mattson RH, Cramer JA, Escueta AVD, et al. A design for the prospective evaluation of the efficacy and toxicity of antiepileptic drugs in adults. *Neurology.* 1983;33(suppl 1):14-25.

7. Cramer JA, Smith DB, Mattson RH, et al. A method of quantification for the evaluation of antiepileptic drug therapy. *Neurology.* 1983;33(suppl 1):26-37.

8. Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondary generalized tonic-clonic seizures. *N Engl J Med.* 1985;313:145-151.

9. Critchley EMR, Vakil SD, Hayward HW, Owen VMH. Dupuytren's disease in epilepsy: result of prolonged administration of anticonvulsants. *J Neurol Neurosurg Psychiatry.* 1976;39:498-503.

10. Féré C, Francillon M. Notes sur la fréquence de la rétraction de l'aponévrose palmaire chez les aliénés. *Rev Med.* 1902;22:539-551.

11. Van der Korst JK, Colenbrander H, Cats A. Phenobarbital and the shoulder-hand syndrome. *Ann Rheum Dis.* 1960;25:553-555.

12. Janz D, Piltz U. Frozen shoulder induced by primidone. In: Oxley J, Janz D, Meinardi H, eds. *Chronic Toxicity of Antiepileptic Drugs.* New York, NY: Raven Press; 1983:155-159.

13. Zachariae J, Cahlerup JV, Olesen E. The electroencephalogram in patients with Dupuytren's contracture. *Scand J Plast Reconstr Surg.* 1970;4:35-40.

14. Froscher W, Hoffman F. Dupuytren's contracture in patients with epilepsy: follow-up study. In: Oxley J, Janz D, Meinardi H, eds. *Chronic Toxicity of Antiepileptic Drugs.* New York, NY: Raven Press; 1983:147-154.

15. Noble J. Connective tissue disorders: discussion. In: Oxley J, Janz D, Meinardi H, eds. *Chronic Toxicity of Antiepileptic Drugs.* New York, NY: Raven Press; 1983:169-173.

16. Blanquart F, Houdent G, Deshayes P. L'algo-dystrophie iatrogene gardenalique. *Sem Hop Paris.* 1974;50:499-503.

17. Horton P, Gerster JC. Reflex sympathetic dystrophy syndrome and barbiturates: a study of 25 cases treated with barbiturates compared with 124 cases treated without barbiturates. *Clin Rheumatol.* 1984;3:493-500.

18. Evans RA. The aetiology of Dupuytren's disease. *Br J Hosp Med.* 1986; 36:198-199.

19. Pojer J, Radivojevic M, Williams TW. Dupuytren's disease: its association with abnormal liver function in alcoholism and epilepsy. *Arch Intern Med.* 1972;129:561-566.

20. Lequesne M. L'algo-dystrophie d'origine chimiothérapique: pseudo-rhumatisme de l'isoniazide, de l'éthionamide, du phénobarbital et de l'iode radioactif. *Sem Hop Paris.* 1967;43:2581-2595.

21. Hurst LC, Badalmente MA, Makowski J, The pathobiology of Dupuytren's contracture: effects of prostaglandins on myofibroblasts. *J Hand Surg.* 1986;11:18-22. Abstract.