Medical Marijuana Program

165 Capitol Avenue, Room 145, Hartford, CT 06106-1630 • (860) 713-6066
E-mail: • **Website:**

Petition to Add a Medical Condition, Medical Treatment or Disease to the List of Debilitating Conditions

INSTRUCTIONS: Please complete each section of this Petition and attach all supportive documents. All attachments must include a title referencing the Section letter to which it responds. Any Petition that is not fully or properly completed will not be submitted to the Board of Physicians.

Please Note: Any individually identifiable health information contained in a Petition shall be confidential and shall not be subject to disclosure under the Freedom of Information Act, as defined in section 1-200, Connecticut General Statutes.

Section A: Petitioner's Information

Name (First, Middle, Last):	[redacted]		
Home Address (including Apartment or Suite #):	[redacted]		
City: [redacted]		State: [redacted]	Zip Code: [redacted]
Telephone Number: [redacted]	E-mail Address: [redacted]		

Section B: Medical Condition, Medical Treatment or Disease

Please specify the medical condition, medical treatment or disease that you are seeking to add to the list of debilitating medical conditions under the Act. Be as precise as possible in identifying the condition, treatment or disease. Fabry disease - major symptom is pain in hands + feet due to fatty acid build up in capillaries other organs affected as well

Section C: Background

Provide information evidencing the extent to which the condition, treatment or disease is generally accepted by the medical community and other experts as a valid, existing medical condition, medical treatment or disease.

- Attach a comprehensive definition from a recognized medical source.
- Attach additional pages as needed.

- FABRY'S disease, ENDSTAGE Renal disease
Gout

Section D: Negative Effects of Current Treatment

If you claim a treatment, that has been prescribed for your condition causes you to suffer (i.e. severe or chronic pain, spasticity, etc.), provide information regarding the extent to which such treatment is generally accepted by the medical community and other experts as a valid treatment for your debilitating condition.

- Attach additional pages as necessary.
- If not applicable, please indicate N/A. Ohmic Pain, depressive Symptoms, Pain From Gout.

Section E: Negative Effects of Condition or Treatment

Provide information regarding the extent to which the condition or the treatments thereof cause severe or chronic pain, severe nausea, spasticity or otherwise substantially limits one or more major life activities.

- Attach additional pages as necessary.

due to severe kidney disease and severe neuropathy - most pain medication does not work or is contra-indicated

Section F: Conventional Therapies

Provide information regarding the availability of conventional medical therapies, other than those that cause suffering, to alleviate suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

Percocet - no help, neurontin - no help, Lyrica - no help
NSAID - contraindicated

Section G: General Evidence of Support for Medical Marijuana Treatment

Provide evidence, generally accepted among the medical community and other experts, that supports a finding that the use of marijuana alleviates suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

SEE Attached
+ effects of marijuana for joint pain + neuropathy

Section H: Scientific Evidence of Support for Medical Marijuana Treatment

Provide any information or studies regarding any beneficial or adverse effects from the use of marijuana in patients with the condition, treatment or disease that is the subject of the petition.

- Supporting evidence needs to be from professionally recognized sources such as peer reviewed articles or professional journals.
- Attach complete copies of any article or reference, not abstracts.

SEE Attached

Section I: Professional Recommendations for Medical Marijuana Treatment

Attach letters in support of your petition from physicians or other licensed health care professionals knowledgeable about the condition, treatment or disease at issue.

SEE Attached

Section J: Submission of Petition

In the event you are unable to answer or provide the required documentation to any of the Sections above (excluding Section D); provide a detailed explanation indicating what you believe is "good cause" for not doing so.

- Attach additional pages as necessary.

I hereby certify that the above information is correct and complete.

My signature below attests that the information provided in this petition is true and that the attached documents are authentic. I formally request that the commissioner present my petition and all supporting evidence to the Board of Physicians for consideration.

Signature	Date Signed:
[redacted]	18-2-14

[redacted]

October 4, 2014

Connecticut Dept of Consumer Protection
Board of Physicians

To Whom It May Concern:

I am writing to request that my disease be placed on the list of acceptable medical condition for receiving medical marijuana. I have Fabry's disease which affects nearly every system in my body. I experience severe pain on a daily basis. I have chronic renal failure, cardiac myopathy with a pacemaker, G-I issues with frequent stomach pains and diarrhea, severe pain in my hands due to poor circulation, and peripheral neuropathy and gout affecting my hands and feet, The pain medication I have been taking has only been partially successful in diminishing the pain and has caused side effects making other symptoms worse.
Please consider granting me a marijuana card so I can live a more comfortable, less painful, and more productful life.
Thank you.

Sincerely,

[redacted]

Clinical features and diagnosis of Fabry disease

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All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Sep 2014. | **This topic last updated:** Jun 05, 2013.

INTRODUCTION — Fabry disease, also called Anderson-Fabry disease, is the second most prevalent lysosomal storage disorder after Gaucher disease. It is an X-linked inborn error of the glycosphingolipid metabolic pathway. This results in accumulation of globotriaosylceramide (Gb3) within lysosomes in a wide variety of cells, thereby leading to the protean manifestations of the disease [1].

This topic provides an overview of Fabry disease, with an emphasis on kidney disease. The cardiac and neurologic manifestations, and the treatment of Fabry disease, are discussed elsewhere. (See "Clinical features, diagnosis, and management of patients with Fabry disease with cardiac disease" and "Neurologic manifestations of Fabry disease" and "Treatment of Fabry disease".)

EPIDEMIOLOGY — The prevalence of Fabry disease is estimated to range from 1:17,000 to 1:117,000 males in Caucasian populations [2-4]. However, the disease is seen across all ethnic and racial groups [4].

The prevalence of Fabry disease is probably underestimated given incomplete ascertainment. This is likely since [4,5]:

- The manifestations of the disease are nonspecific.
- The diagnosis is often not considered by physicians, given the rarity of the disease.
- The wrong diagnosis is often made initially. As an example, in the 366 European patients with Fabry disease participating in the Fabry Outcome Survey, the mean delay to correct diagnosis after symptom onset was estimated to be 13.7 and 16.3 years for males and females, respectively [5].

Fabry disease as a cause of ESRD — Renal manifestations occur in approximately 50 percent of affected patients by the age of 35 years, and the incidence increases significantly with age. A significant fraction of patients eventually develops end-stage renal disease (ESRD). As an example, all male patients in one study who survived to the age of 55 years developed ESRD [2]. However, in a registry of over 2000 patients with Fabry disease (mean age 37 to 40 years), the prevalence of ESRD was much lower (14 percent in men and 2 percent in women) [6]. By age 55 years, only 32 percent of men and 19 percent of women developed renal events, which ranged from new onset chronic kidney disease (defined as a glomerular filtration rate less than 60 mL/min/1.73 m2) to end-stage renal disease.

The prevalence of Fabry disease in dialysis populations has been examined in several screening studies. Random screening has identified fewer than 1 percent of hemodialysis patients as having Fabry disease, most of whom were already known to have the disease [7-13]. The following findings from different regions are illustrative:

- According to the 2010 annual data report by United States Renal Data System, Fabry disease accounted for only 95 new cases of ESRD between 2005 and 2009 (including 80 males and 15 females), which represents approximately 0.02 percent of the incident patients each year [7].
- In a Japanese study, six of 514 (1.2 percent) consecutive males on dialysis had low leukocyte alpha-Gal A levels, and were found to have a gene mutation [8]. Another Japanese study of 696 consecutive patients (295 females) found only four males and one female (0.7 percent) to have Fabry disease, and three were already known to have it [11].

- In a nationwide screen of the Austrian dialysis population, 85 of 2480 patients (3.4 percent, similar proportions in male and female) had a positive blood spot test with low alpha-Gal A levels [9]. Among these patients, only 5 women and 10 men had confirmed low leukocyte alpha-Gal A levels, representing 0.5 percent of the screened population. Only four males (0.16 percent) had the gene mutation, three of whom were already diagnosed.

A voluntary Fabry disease registry has been established to better understand the epidemiology and prognosis of the disease (www.lsdregistry.net/fabryregistry or 1-800-745-4447).

PATHOPHYSIOLOGY — The metabolic defect in Fabry disease is deficiency of the lysosomal hydrolase alpha-galactosidase A (alpha-Gal A), which catalyzes the hydrolytic cleavage of the terminal galactose from globotriaosylceramide (Gb3) [14]. The alpha-Gal A protein is encoded by a 12-kb gene mapped to the long arm (Xq22.1 region) of the X chromosome [15]. Several hundred mutations in the alpha-Gal A gene have thus far been identified [16,17]. Most kindreds have specific, or private, mutations, and de novo mutations are rare [18].

Gb3 is an intermediate in the degradative pathway of globoside. Globoside, a major glycosphingolipid in the red cell membrane and the kidney, is composed of ceramide attached to three sugar residues and an N-acetylgalactosamine residue (ceramide-Glc-Gal-Gal-GalNAc). Globoside is metabolized in lysosomes, particularly in the spleen, liver, and bone marrow. In the absence of significant alpha-Gal A activity, Gb3 accumulates in various cells and tissues. Tissue accumulation of Gb3 is inversely correlated with residual alpha-Gal A activity in leukocytes [2].

The accumulation of Gb3 is particularly prominent in the vascular endothelium (at levels up to 460-fold higher than normal), vascular smooth muscle cells, and pericytes [2,19,20]. The deposition of glycosphingolipid in these cells may lead to vascular occlusion, ischemia, and infarction. However, it is possible that accumulation of Gb3 in other cell types within the vessel wall may be important. As an illustrative example, enzyme replacement therapy in adults clears Gb3 from the endothelium but not from the rest of the vessel, and does not reduce the incidence of stroke [21].

Accumulation of Gb3 in autonomic ganglia, dorsal root ganglia, renal glomerular, tubular and interstitial cells, cardiac muscle cells, vascular smooth muscle cells, valvular fibrocytes, and cardiac conduction fibers may lead to the myriad other manifestations of the disease. Accumulation in the cornea also occurs, but is clinically silent. The actual clinical involvement varies significantly among different organs, which likely represents various rates of sphingolipid metabolism in different tissues [22].

Gb3 deposition may be only partially responsible for the manifestations of the disease. Other as yet unexplained factors might also contribute, since disease manifestations may be present in the absence of severe deposits. In one report of 57 symptomatic female patients with confirmed Fabry genotype who underwent a skin biopsy, only one patient had visible glycolipid accumulation in endothelial cells by light microscopy, and 10 to 50 percent had mild accumulation in other cell types [23]. However, cardiac, renal or cerebrovascular abnormalities were documented in 90 percent. Electron microscopy and examination of other organs such as kidney or heart were not done in this study.

Pathophysiology of renal disease — Gb3 accumulation in the kidney is inversely correlated with residual alpha-Gal A activity in leukocytes [2]. In addition, the magnitude of renal Gb3 content correlates positively with the severity of renal pathologic changes and inversely with kidney function. Thus, accumulation of Gb3 in the kidney is probably responsible for the renal manifestations of the disease. (See 'Renal manifestations' below.)

Gb3 accumulation in the kidney occurs preferentially in the glomeruli (especially podocytes, but also in endothelial, and mesangial cells), and in the distal tubule. The predilection for these two locations may explain the early renal manifestations of proteinuria and polyuria. In children with Fabry disease, for example, podocyte Gb3 accumulation was strongly associated with foot process width and the degree of proteinuria, implicating glomerular involvement in the early onset proteinuria observed in this disease [24].

The pathophysiology underlying the formation of renal sinus cysts, another manifestation in patients with Fabry disease, is unknown. (See 'Renal sinus cysts' below.) The presence of cysts is not related to residual alpha-Gal A activity, renal function, or level of proteinuria. It is unclear whether the cysts contain Gb3, or whether this is due to lymphatic overload or other processes.

CLINICAL PRESENTATION — Although variability exists, the symptoms of Fabry disease tend to appear in a predictable order in classically affected males (table 1) [18,20,25].

Overview of clinical manifestations — Clinical manifestations begin in childhood or adolescence, and include [2,5,20]:

- Severe neuropathic or limb pain, which may be precipitated by stress, extremes of heat or cold, and physical exertion. Neuropathic symptoms occur in more than 75 percent of patients with a mean age of onset of 10 years. (See "Neurologic manifestations of Fabry disease".)
- Telangiectasias and angiokeratomas, the latter commonly in groin, hip and periumbilical areas, are characteristic (picture 1 and picture 2). Thickening of the lips and bulbous nose have also been described. Dermatologic manifestations of Fabry disease occur in more than 70 percent of patients with a mean age of onset of 17 years.
- Renal manifestations such as proteinuria, polyuria, and polydipsia or otherwise unexplained renal insufficiency are common. Renal disease, particularly proteinuria, occurs in more than 80 percent of patients with a mean age of diagnosis of 35 to 40 years. (See 'Renal manifestations' below.)
- Other nonspecific manifestations, which tend to worsen in early adulthood, include heat, cold, and exercise intolerance, hypohidrosis (or hyperhidrosis [26,27]), lymphadenopathy, and gastrointestinal symptoms such as abdominal pain and diarrhea. These manifestations occur in 50 to 70 percent of patients, often by the fourth decade.

In adulthood, there is progressive cardiac and cerebral involvement, which accounts for the majority of deaths associated with Fabry disease [28]:

- Cardiac involvement includes concentric left ventricular hypertrophy, heart failure, coronary artery disease, aortic and mitral valve abnormalities, and conduction abnormalities. Cardiac manifestations occur in more than 80 percent of patients with Fabry disease, with a mean age of onset of 42 years. In some patients, these manifestations, particularly left ventricular hypertrophy, are the only recognized manifestations of the disease. Fabry disease is a potential cause of unexplained left ventricular hypertrophy. (See "Clinical features, diagnosis, and management of patients with Fabry disease with cardiac disease", section on 'Ventricular hypertrophy'.)
- Cerebrovascular involvement may lead to transient ischemic attacks and strokes, and can cause a wide range of neurologic symptoms, including blindness. In addition, enlargement of large cranial arteries (dolichoectasia) may occur. Transient ischemic attacks and strokes occur in approximately 25 percent of patients with a mean age of onset of 40 years. (See "Neurologic manifestations of Fabry disease".)

The age of symptom onset is more consistent in male hemizygotes than in female heterozygotes; approximately 80 percent of males have neurologic, dermatologic and cardiac manifestations by the second, third and fifth decades of life, respectively [5]. Males with atypical variants may present even later in life, diagnosed during evaluations for cardiomegaly or proteinuria [18].

Clinical manifestations in heterozygous females vary widely from no apparent clinical disease to full expression of the disease, possibly related to random X-chromosome inactivation, although this is not proven [29,30]. Up to 90 percent may have clinical manifestations [23].

Renal manifestations — Renal manifestations occur in at least 50 percent of male patients and about 20 percent of female patients [1,6]. When patients with Fabry disease present with renal manifestations, the principal findings are proteinuria and progressive renal insufficiency. Uncommonly, patients complain of polyuria and polydipsia, or are discovered by the presence of renal sinus cysts on an imaging study.

Proteinuria — Proteinuria, which may be tubular or glomerular in origin, may begin in the early teen years, but more typically appears during early adulthood. As an example, a long-term natural history study from the National Institutes of Health (NIH) reported proteinuria among 66 of 78 (85 percent) male patients with renal disease, with the average age of onset being 34 years (range 14 to 55) [2]. Nephrotic-range proteinuria was uncommon (18 percent of those with renal disease), and only a fourth of them developed nephrotic syndrome. However, among those with progressive kidney failure, 80 percent had nephrotic proteinuria.

Adult males with Fabry disease who have the highest levels of proteinuria (urine protein/creatinine ratio [UP/Cr] >1.5 gm/gm) also have the fastest decline in kidney function [31,32]. However, proteinuria is much less closely associated with renal function decline in adult female Fabry patients [31,32]. Thus, the concept that proteinuria per se is a direct promoter of progression in Fabry disease may be incorrect.

In addition to protein, the urine may contain oval fat bodies (tubular epithelial cells with lipid inclusions) with a lamellar structure and a Maltese cross pattern under polarized urine microscopy. (See "Urinalysis in the diagnosis of kidney disease", section on 'The assessment of lipiduria'.)

Chronic kidney disease — In untreated patients with Fabry disease, progressive CKD develops over time, sometimes resulting in ESRD. In the previously described natural history study from the NIH, the following findings were reported [2]:

- Forty-eight percent developed CKD (defined as a serum creatinine concentration ≥1.5 mg/dL [133 µmol/L]), which occurred at a median age of 42 years. In those with the lowest enzyme activity, CKD developed at an earlier mean age (22 versus 47 years).
- Twenty-four patients overall (29 percent), and all who survived to the age of 55 years, eventually developed ESRD (median age 47 years). Progression to ESRD from the diagnosis of CKD occurred over an average of four years (range 1 to 13), corresponding to a mean rate of decline in glomerular filtration rate (GFR) of 12 mL/min per 1.73 m2 per year. Once CKD developed, the rate of progression to ESRD did not vary with age.

Similar findings with respect to CKD and ESRD were reported in an English cohort study of 98 hemizygous males [20]. Eighty-four percent had proteinuria and 47 percent had decreased kidney function. However, the 31 percent of patients who developed ESRD did so at a younger age than in the study from the United States, with a mean age of dialysis initiation of 37 years; the youngest presented at 18 years of age.

However, other studies have reported a much lower incidence of ESRD among older individuals [6]. In a registry of over 2000 patients with Fabry disease (mean age 37 to 40 years), only 32 percent of men and 19 percent of women who were 55 years of age or older developed renal events, which ranged from new onset chronic kidney disease (defined as a glomerular filtration rate less than 60 mL/min/1.73 m2) to end-stage renal disease.

Although there are some conflicting observations in females, increased proteinuria in male patients with Fabry disease appears to correlate with an increased risk of progression to ESRD [2,31-35].

The effect of enzyme replacement therapy on the progression incidence and progression of CKD is discussed elsewhere. (See "Treatment of Fabry disease".)

Isosthenuria and Fanconi syndrome — Relative to other segments, the distal tubules are preferentially affected, leading to decreased urinary concentrating ability [36] and polyuria. Polyuria and polydipsia may be the earliest functional symptoms of Fabry renal disease [37]. Gb3 deposition in proximal tubules may also produce Fanconi syndrome, which includes the manifestations of proximal renal tubular acidosis. (See "Etiology and diagnosis of distal (type 1) and proximal (type 2) renal tubular acidosis".)

Renal sinus cysts — The prevalence of renal sinus and parapelvic cysts is increased in patients with Fabry disease relative to healthy controls [38,39]. As an example, in one study of 24 patients with Fabry disease and 19 age-matched healthy controls, 50 percent of Fabry patients compared with only 7 percent of controls had renal sinus cysts, respectively [38]. In contrast, simple cysts located in renal parenchyma are commonly found in the adult population [40]. Thus, the incidental discovery of multiple renal sinus cysts with an imaging study should raise the possibility of Fabry disease in the appropriate clinical setting.

Hypertension — In the NIH study, only 30 percent of 105 subjects developed hypertension, with over one-half developing increased blood pressure only after the onset of CKD [2]. Overall, the onset of CKD was followed by the development of hypertension, which was then closely followed by the onset of ESRD before death ensued.

INITIAL EVALUATION — Although this section will focus on the renal evaluation, most of the ensuing discussion is generally relevant to Fabry disease.

When to suspect Fabry disease — An evaluation for Fabry disease should be performed in males or females with the following clinical features suggestive of the diagnosis, particularly:

- Intermittent episodes of severe pain in the extremities (acroparesthesias)
- Cutaneous vascular lesions (angiokeratomas)
- Diminished perspiration (hypohidrosis)
- Left ventricular hypertrophy of unknown etiology in young adulthood
- Stroke of unknown etiology in young adulthood
- Chronic kidney disease of unknown etiology in young adulthood
- Multiple renal sinus cysts discovered incidentally

A family history suggestive of the disorder is particularly helpful. (See 'Clinical presentation' above and 'Renal manifestations' above.)

We also recommend an evaluation in the following patients:

- Females known or suspected to be carriers
- Some family members of newly diagnosed patients

Specific issues related to case finding in family members of patients with Fabry disease are presented below (see 'Evaluation of family members' below).

Initial assessment — An initial evaluation should consist of the following [18,25,30]:

- Detailed past medical history and review of systems. Clinical symptoms or signs such as neuropathic pain, heat intolerance (usually associated with exercise intolerance and avoidance of outdoors in summer months), decreased tear, saliva or sweat production, diarrhea, abdominal pain, angiokeratomas and foamy urine should be carefully documented at baseline. Any history of transient ischemic attacks or strokes (particularly involving the posterior circulation), and myocardial disease should be thoroughly explored.

- Detailed family history that focuses on relatives with unexplained neurologic disease or kidney failure that was transmitted as an X-linked trait. In the NIH series, family history contributed to the diagnosis in 46 percent of patients.

- Careful physical examination, looking for angiokeratomas, telangiectasias, hypo- or anhydrosis, corneal opacity, edema, abnormal cardiac examination (evidence of left ventricular hypertrophy, arrhythmia). Asymptomatic characteristic corneal opacities (cornea verticillata) that do not affect visual acuity and retinal and conjunctival vascular tortuosity are present in almost all Fabry males [1]. Formal slit-lamp examination may be necessary to appreciate the corneal opacities.

- Examination of urine sediment and measurement of renal function. With renal involvement, there may be oval fat bodies (degenerating tubular epithelial cells with lipid inclusions) with a lamellar structure and a Maltese cross pattern under polarized microscopy (picture 3); this is similar to what may be seen with nephrotic range proteinuria of any cause. (See "Urinalysis in the diagnosis of kidney disease" and "Urinalysis in the diagnosis of kidney disease", section on 'The assessment of lipiduria'.)

- Electrocardiogram to evaluate for left ventricular hypertrophy and conduction defects.

DIAGNOSIS — In the setting of clearly established family history and classic phenotype, the diagnosis can usually be confirmed **in males** if there is low alpha-Gal A activity in leukocytes or plasma [2,41,42]. Analysis of plasma alpha-galactosidase may be less sensitive than assay of enzyme activity in leukocytes [43].

Mutation analysis of the alpha-Gal A gene is required to make the diagnosis **in female carriers** (unless the woman is an obligate heterozygote [ie, the father is known to have Fabry]), and in males and females with atypical presentations or marginal alpha-Gal A levels [18,30,44]. Rarely, the diagnosis is made by biopsy of the skin or kidney when other means of diagnosis are unavailable. On the other hand, patients may be incidentally discovered to have Fabry disease if a kidney biopsy is performed to evaluate chronic kidney disease.

Diagnosis in classically affected males — Measurement of leukocyte alpha-Gal A activity is the standard enzymatic test at most laboratories. The sensitivity and specificity of the alpha-Gal A assay using leukocytes approaches 100 percent in males, but the assay will identify less than 50 percent of female carriers. Based on the available knowledge, neither ESRD nor dialysis affects the enzyme assay.

Although different methods have been used to describe the results, enzymatic activity level is most often expressed as the percent of normal [2]. The enzymatic level can vary by population tested:

- Alpha-Gal A activity in leukocytes is undetectable in over 50 percent of hemizygous males, and is usually less than four percent of normal control levels in the remainder [2].
- Levels in female carriers range from normal to very low [37].
- Cardiac variants, a form of atypical disease, have one to ten percent of normal activity levels.

Diagnosis in females or males with atypical presentations — We recommend genetic testing in females and males with marginal levels of alpha-Gal A activity. Although not required for the diagnosis in most patients, genotyping is recommended for all Fabry families since this knowledge may be particularly relevant for future therapies utilizing synthetic chaperones [45]. Only one member of each affected family needs to be genotyped. Since more than 300 distinct mutations have thus far been identified, identification of a mutation in a new family requires essentially complete resequencing of the gene. Genetic analysis is only done at selected laboratories (refer to www.genetests.org) [30].

Tissue diagnosis in rare settings — In some cases, biopsy of skin or culture of skin fibroblasts may be helpful in establishing the diagnosis, but is usually done only if no other means of diagnosis are available. Skin biopsy can demonstrate the characteristic glycolipid deposits in a relatively non-invasive way.

Kidney biopsy may be helpful in establishing the diagnosis, but it is not typically necessary. The diagnosis is sometimes made by accident when a kidney biopsy is obtained to diagnose the cause of proteinuria and/or decreased kidney function [44,46]. A kidney biopsy may be of particular use when patients have nephrotic syndrome, gross hematuria, or other symptoms that require exclusion of other diagnoses. (See 'Renal pathology' below.)

Renal pathology — Kidney biopsy findings by light microscopy and electron microscopy are characteristic in Fabry disease, whereas immunofluorescence staining does not contribute to the diagnosis. Glycolipid accumulation is observed throughout the kidney:

- Light microscopy shows vacuolization of visceral glomerular epithelial cells (podocytes) and distal tubular epithelial cells [2]. This is consistent with the described pattern of glycolipid accumulation, with podocytes and distal tubular cells showing the largest amount. Smaller deposits in cells of the mesangium glomerular endothelium [22], proximal tubule (picture 4A-B) [22,47,48], and in the endothelium of peritubular capillaries and arteries may be difficult to appreciate by routine light microscopy.
- On electron microscopy, deposits of Gb3 appear within enlarged secondary lysosomes as lamellated membrane structures, called myeloid or zebra bodies (picture 5). These inclusions, composed of concentric layers with a periodicity of 3.5 to 5 nm and with an onion skin appearance, are considered a **hallmark** of glycolipid storage disorders [49]

The ultrastructural findings on kidney biopsy are highly characteristic and frequently point to the diagnosis. However, lamellar inclusions have been described in other conditions, including silicosis and gentamicin toxicity [50-53]. The location of the inclusions is sometimes helpful in making the distinction between these diseases. Lamellar inclusions associated with gentamicin occur in proximal tubules, whereas in Fabry disease, the inclusions are most striking in podocytes and distal tubules.

Nonspecific findings in patients with more advanced disease may include focal segmental and global glomerulosclerosis and tubulointerstitial fibrosis, with mesangial deposits staining for C3 and IgM [54]. Foam cells may also be seen but are not diagnostic of Fabry disease, as they may be seen in other lysosomal storage diseases (where lipid is in podocytes) and proteinuric states (where lipid is primarily in macrophages) [55].

Thus, renal Gb3 content is significantly higher, and glomerular and tubulointerstitial changes and kidney function worse, in patients with undetectable alpha-Gal A activity compared with those with greater than 1 percent of normal activity.

DIFFERENTIAL DIAGNOSIS — Fabry disease is often misdiagnosed, given its wide range of nonspecific clinical manifestations and relative rarity. It has recently been termed "The New Great Imposter" [56]. Because of its rarity, patients with Fabry disease are often initially diagnosed with some other condition. The most commonly considered initial diagnoses in patients with Fabry disease in the Fabry Outcome Survey were [4,5]:

- Rheumatologic conditions including dermatomyositis or rheumatic fever. However, the characteristic heliotrope rash and elevated serum muscle enzymes distinguish juvenile onset dermatomyositis from Fabry disease. In addition, the pain and dermatologic symptoms of acute rheumatic fever are typically self-limited, lasting less than a month. (See "Diagnosis of juvenile dermatomyositis and polymyositis" and "Clinical manifestations and diagnosis of acute rheumatic fever".)
- Arthritis. However, Fabry disease is not characterized by synovial inflammation. (See "Diagnosis and differential diagnosis of rheumatoid arthritis".)
- Neuropsychological disease. However, many common manifestations of Fabry, including proteinuria, left ventricular hypertrophy, and angiokeratomas, are not typical in patients with psychiatric disease. (See "Neurologic manifestations of Fabry disease".)
- Fibromyalgia. As above, many common manifestations of Fabry, including proteinuria, left ventricular hypertrophy, and angiokeratomas, are not common in patients with fibromyalgia. (See "Clinical manifestations and diagnosis of fibromyalgia in adults".)
- Erythromelalgia. However, patients with Fabry disease do not have thrombocythemia, which can cause pain in the extremities of patients with polycythemia vera and essential thrombocythemia. (See "Clinical manifestations and diagnosis of polycythemia vera", section on 'Erythromelalgia'.)
- Hereditary hemorrhagic telangiectasia. Although patients with Fabry disease may have telangiectasias, they do not typically develop spontaneous epistaxis or gastrointestinal bleeding, as do patients with hereditary hemorrhagic telangiectasia. (See "Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)".)
- Meniere disease. Although tinnitus is present in nearly 40 percent of patients with Fabry disease, the presence of neuropathic pain, angiokeratomas, and proteinuria helps distinguish it from Meniere disease. (See "Meniere disease".)
- Multiple sclerosis. However, the presence of angiokeratomas, proteinuria, and left ventricular hypertrophy, which are not features of multiple sclerosis, provide clues to Fabry disease. (See "Clinical features of multiple sclerosis in adults".)
- Irritable colon. However, neuropathic pain, angiokeratomas, and proteinuria are not features of irritable bowel syndrome. (See "Irritable bowel syndrome in patients with inflammatory bowel disease".)
- Idiopathic hypertrophic cardiomyopathy. Echocardiography may be able to distinguish patients with Fabry disease from those with other causes of left ventricular hypertrophy. (See "Clinical features, diagnosis, and management of patients with Fabry disease with cardiac disease".)
- Kidney failure of unknown etiology. When occurring in a young individual, kidney disease of unknown etiology should prompt an evaluation for Fabry disease, particularly other common manifestations (eg, neuropathic pain) and a family history of kidney failure are present. (See 'When to suspect Fabry disease' above.)

As a result, the diagnosis of Fabry disease in patients without a known family history of the disorder is usually made by specialists and subspecialists: dermatologists (28 percent); neurologists (23 percent); nephrologists (19 percent); rheumatologists (2 percent); and cardiologists (2 percent) [2]. Consideration of Fabry disease as a possibility is the major hurdle to making the correct diagnosis in such patients.

FOLLOW-UP ASSESSMENT — Once diagnosed, patients with Fabry disease, or asymptomatic carriers, should be followed closely using an interdisciplinary approach that involves routine care by nephrology, cardiology, and neurology, with input from dermatology and ophthalmology as required [18,57]:

- Annual reevaluation with documentation of any clinical symptoms or signs. The annual exams should also include routine hematology and chemistry profiles, urinalysis, urinary protein to creatinine ratio or albumin to creatinine ratio, and an estimation of renal function such as estimated glomerular filtration rate or measurement of the creatinine clearance. (See "Assessment of kidney function" and "Calculation of the creatinine clearance".)
- Echocardiography and electrocardiography to detect or monitor cardiac abnormalities at least every two years.
- Asymptomatic female carriers should also have a complete baseline evaluation as above and should be reevaluated every three to five years, with increasing frequency with age. Atypical males with Fabry disease should be evaluated and monitored annually similar to those classically affected.

EVALUATION OF FAMILY MEMBERS — In families known to have Fabry disease, we suggest the following approach in individuals at risk [30]:

- At risk or symptomatic male relatives of an affected individual. These males should be screened with an enzymatic assay (blood or leukocyte), even if asymptomatic. If deficient alpha-Gal A activity is found, the individual should undergo comprehensive genetic analysis to identify the lesion, unless the mutation has been identified in the affected relative. (See 'Diagnosis in females or males with atypical presentations' above.)
- At risk female relatives of an affected individual, a female with a family history of Fabry disease, or a female with symptoms suggestive of Fabry disease. When testing women, the high false negative rate of alpha-Gal A testing in female carriers must be recognized [18,44]. Given the high variability of enzyme activity level in women, genetic testing of women with normal alpha-Gal A levels should be strongly considered.

Although available, routine prenatal screening is **not** recommended, as there are no data to suggest efficacy of initiating enzyme replacement therapy during infancy [30]. Prenatal testing involves measuring alpha-Gal A activity in fetal cells obtained through amniocentesis or chorionic villous sampling; the latter allows earlier (9 weeks versus 16 weeks) and faster test results (hours versus 2 weeks). However, a genetic mutation analysis must also be done because the sample may be contaminated with maternal tissue or female fetuses may have variable residual enzymatic activity.

Some have advocated screening by testing for elevated urinary excretion of Gb3. Mass spectrometry is one available method, with abnormally high levels being relative to healthy controls tested in the same lab [58,59]. However, urine Gb3 may not always be elevated in heterozygotes and remains a suboptimal marker of Fabry disease. We do not advocate its use either for screening or monitoring treatment response. Screening by testing for urinary lyso-Gb3, rather than Gb3, may prove more promising as a diagnostic and disease severity indicator [60].

SUMMARY AND RECOMMENDATIONS

- Fabry disease, also called Anderson-Fabry disease, is the second most prevalent lysosomal storage disorder after Gaucher disease. It is an X-linked inborn error of the glycosphingolipid metabolic pathway. The metabolic defect in Fabry disease is deficiency or defect in the lysosomal hydrolase alpha-galactosidase A (alpha-Gal A), which catalyzes the hydrolytic cleavage of the terminal galactose from globotriaosylceramide (Gb3). This results in accumulation of Gb3 within lysosomes in a wide variety of cells, such as vascular endothelium, autonomic and dorsal root ganglia, renal glomerular, tubular and interstitial cells, cardiac muscle cells, vascular smooth muscle cells, valvular fibrocytes, and cardiac conduction fibers. Accumulation of Gb3 in these cells may produce the many manifestations of the disease. (See 'Introduction' above and 'Pathophysiology' above.)
- The prevalence of Fabry disease is estimated to range from 1:17,000 to 1:117,000 males in Caucasian populations, although the disease is seen across all ethnic and racial groups. The prevalence of Fabry disease is probably underestimated given incomplete ascertainment due, in part, to the nonspecific manifestations of the disease. (See 'Epidemiology' above.)

- Renal manifestations occur in approximately 50 percent of affected male patients by the age of 35 years, and the incidence increases significantly with age. A majority of male patients and a significant fraction of female patients eventually develop end-stage renal disease. Random screening has identified that 0.36 to 1.5 percent of hemodialysis patients have Fabry disease, many of whom were already known to have the disease. (See 'Fabry disease as a cause of ESRD' above.)
- Although variability exists, the symptoms of Fabry disease tend to appear in a predictable order, beginning in childhood or adolescence, in classically affected males (table 1) (see 'Overview of clinical manifestations' above):
    - Severe neuropathic or limb pain, which may be precipitated by stress, extremes of heat or cold, and physical exertion.
    - Telangiectasias and angiokeratomas, the latter commonly in groin, hip and periumbilical areas, are characteristic (picture 1 and picture 2). Thickening of the lips and bulbous nose have also been described.
    - Proteinuria, polyuria, and polydipsia or otherwise unexplained renal insufficiency.
    - Heat, cold, and exercise intolerance, hypohidrosis (or hyperhidrosis), lymphadenopathy, and gastrointestinal symptoms such as abdominal pain and diarrhea.
    - In adulthood, there is a high risk of progressive cardiac and cerebral involvement, especially in males.
- Approximately 80 percent of males have neurologic, dermatologic and cardiac manifestations by the second, third and fifth decades of life, respectively. Males with atypical variants may present even later in life, while clinical manifestations in heterozygous females vary widely from no apparent clinical disease to full expression of the disease, possibly related to random X-chromosome inactivation. (See 'Overview of clinical manifestations' above.)
- Renal manifestations occur in at least 50 percent of male patients and about 20 percent of female patients. When patients with Fabry disease present with renal manifestations, the principal findings are proteinuria and progressive renal insufficiency. Less commonly, patients complain of polyuria and polydipsia, or are discovered by the presence of renal sinus cysts on an imaging study. (See 'Renal manifestations' above.)
- Fabry disease should be suspected in males or females with the following features (See 'When to suspect Fabry disease' above.):
    - Intermittent episodes of severe pain in the extremities (acroparesthesias)
    - Cutaneous vascular lesions (angiokeratomas)
    - Diminished perspiration (hypohidrosis)
    - Left ventricular hypertrophy of unknown etiology in young adulthood
    - Stroke of unknown etiology in young adulthood
    - Chronic kidney disease of unknown etiology in young adulthood
    - Multiple renal sinus cysts discovered incidentally
- An initial evaluation should consist of a detailed medical history and physical examination looking for suggestive clinical symptoms, a family history of unexplained neurologic or kidney disease transmitted in an X-linked pattern, angiokeratomas, telangiectasias, hypohidrosis, corneal opacities, and an abnormal cardiac exam. Laboratory studies should include a urinalysis looking for proteinuria, an assessment of renal function, and an electrocardiogram. (See 'Initial assessment' above.)
- In the setting of clearly established family history and classic phenotype, the diagnosis is can usually be confirmed **in males** by a low alpha-Gal A activity in leukocytes or plasma. Mutation analysis of the alpha-Gal A gene is required to make the diagnosis **in female carriers** unless the woman is an obligate heterozygote (ie, the father is known to have Fabry), and in patients with atypical presentations or who have residual alpha-Gal A levels. (See 'Diagnosis' above.)

- The most commonly considered initial diagnoses in patients with Fabry disease were rheumatologic conditions or rheumatic fever. Other often-considered diagnoses include arthritis, neuropsychological disease, fibromyalgia, dermatomyositis, erythromelalgia, hereditary hemorrhagic telangiectasia, Meniere disease, multiple sclerosis, irritable colon, idiopathic hypertrophic cardiomyopathy, and kidney failure of unknown etiology. (See 'Differential diagnosis' above.)

- Once diagnosed, patients with Fabry disease, or asymptomatic carriers, should be followed closely using an interdisciplinary approach that involves routine care by nephrology, cardiology, and neurology, with input from dermatology and ophthalmology as required. (See 'Follow-up assessment' above.)

- In families known to have Fabry disease, we suggest screening at risk or symptomatic male relatives of an affected individual, at risk female relatives of an affected individual, females with a family history of Fabry disease, and females with symptoms suggestive of Fabry disease. (See 'Evaluation of family members' above.)

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Topic 7195 Version 14.0

GRAPHICS

Clinical manifestations of Fabry disease

Childhood
Pain, numbness of fingers and toes
Telangiectasias on ears, conjunctiva
Blue-black angiomatous macules or papules
Edematous upper eyelids
Raynaud phenomenon
Ophthamologic abnormalities
Early adulthood
Extensive telangectasias, angiokeratomas
Albuminuria, hematuria, oval fat bodies in urine
Edema
Fever, heat collapse, anhidrosis
Lymphadenopathy
Isothermia
30-40 years of age
Cardiac disease: coronary conduction defects, mitral insufficiency
Renal insufficiency
Cerebrovascular attacks
Neurologic findings suggesting multiple sclerosis

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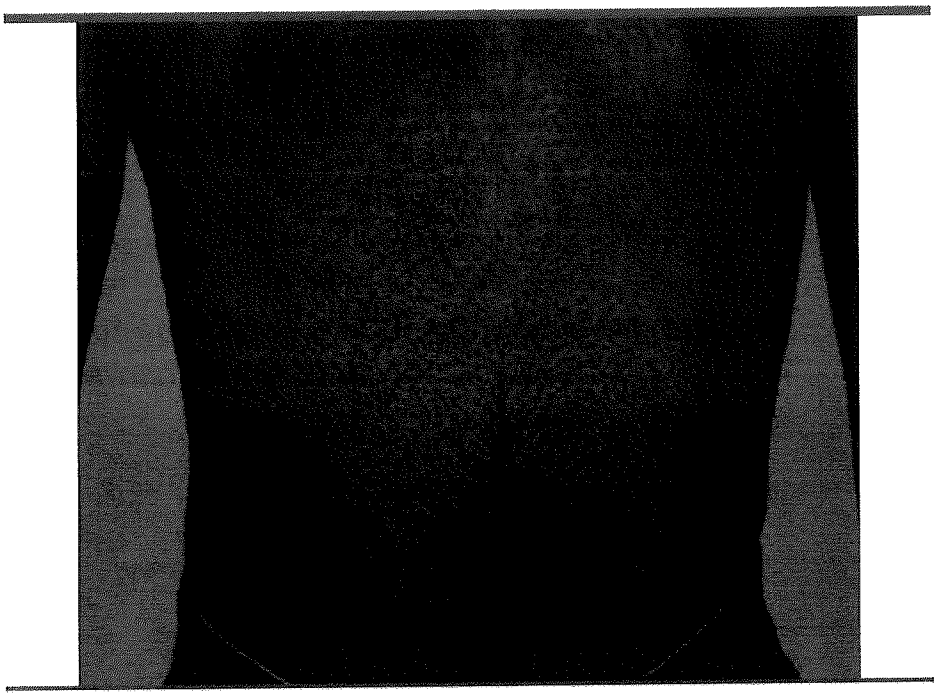
Graphic 57531 Version 3.0

Angiokeratomas are distributed in a typical symmetrical fashion on the torso



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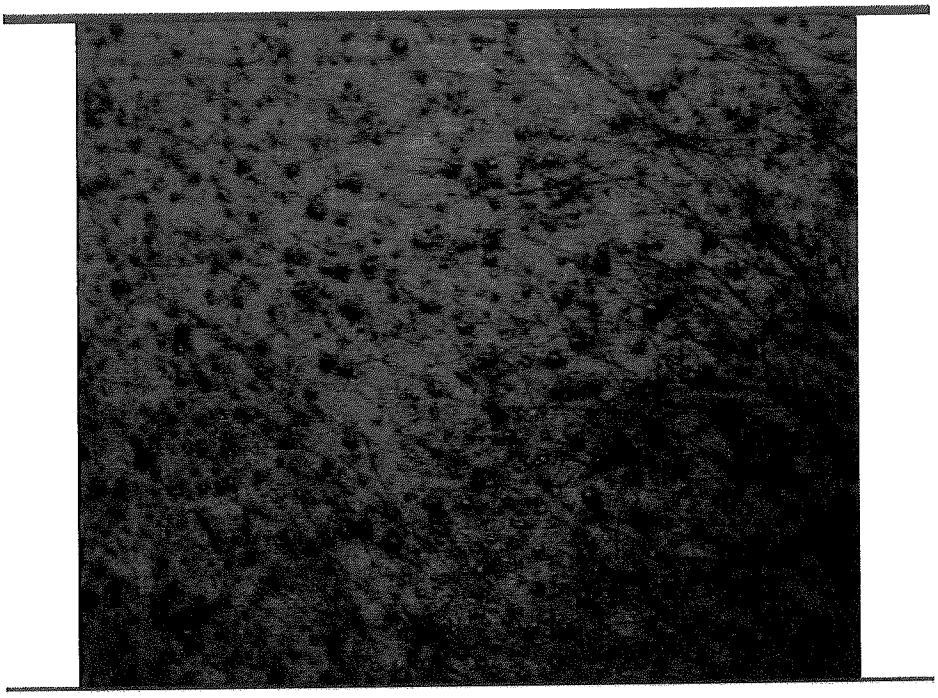
Graphic 81624 Version 2.0

Higher power view demonstrates the elevated papules



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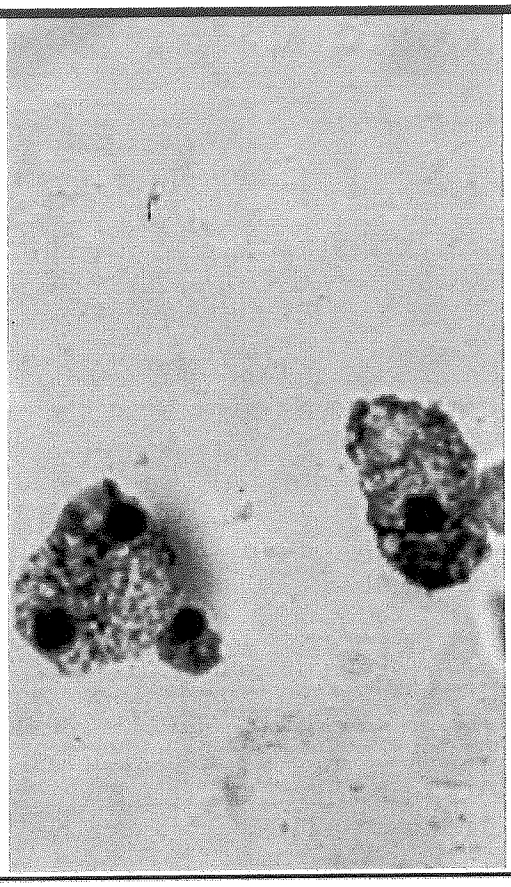
Graphic 71039 Version 2.0

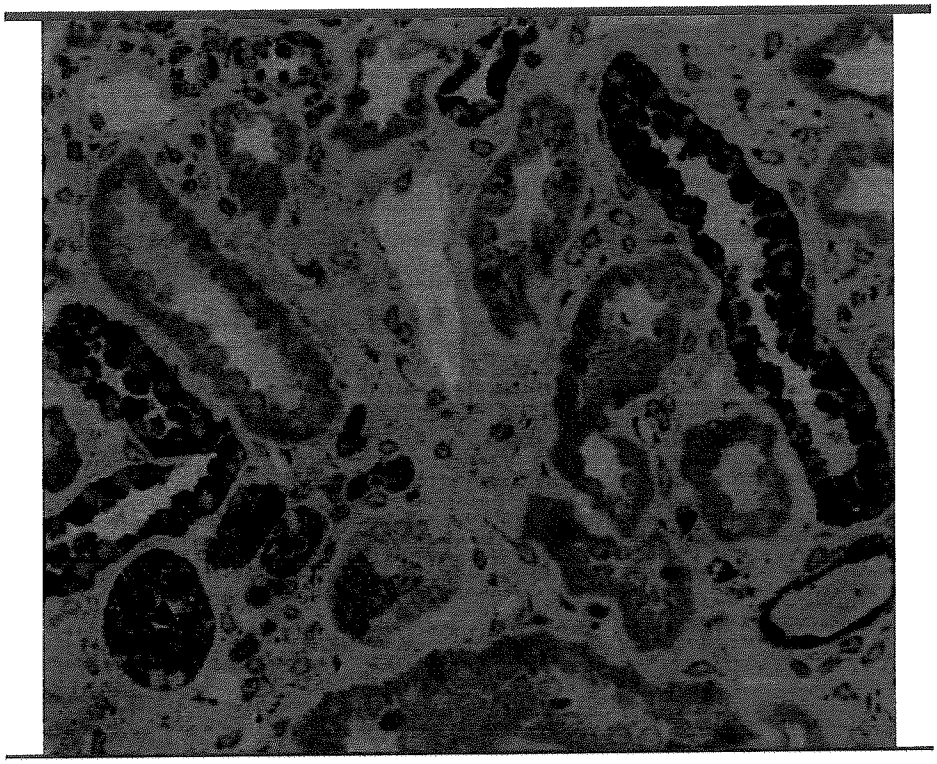
Vacuolated uroepithelial cells



Urine showing vacuolated urinary epithelial cells (oval fat bodies) in a Fabry patient (Papanicolaou stain, original magnification X160).

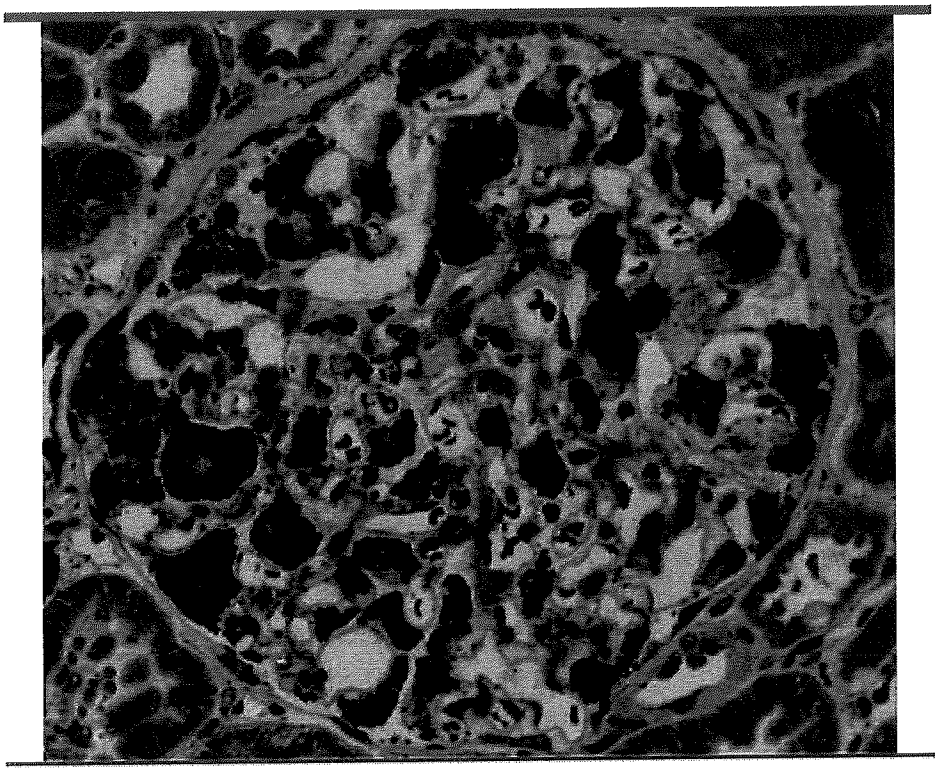
Graphic 54906 Version 6.0

Plastic embedded renal tissue demonstrating glycolipid inclusion bodies in distal tubules, with relative sparing of proximal tubules, and interstitial fibrosis (toluidine blue stain, original magnification X80)



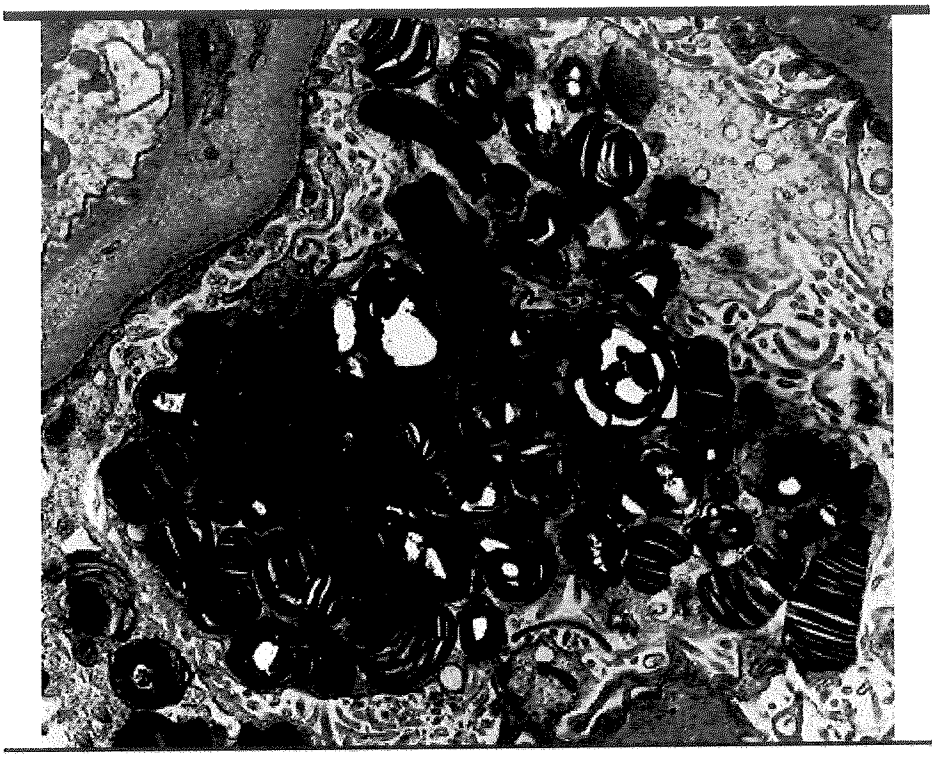
Graphic 54672 Version 6.0

Plastic embedded tissue showing in site deposition of glycolipid in glomerular podocytes (toluidine blue stain, original magnification X80)



Graphic 75690 Version 7.0

Electron micrograph showing lamellar osmophilic inclusions in a glomerular podocyte



The foot processes are intact. (Original magnification X20,000).

Graphic 68849 Version 7.0

Disclosures

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Conflict of interest policy

Clinical features and diagnosis of Fabry disease

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INTRODUCTION — Fabry disease, also called Anderson-Fabry disease, is the second most prevalent lysosomal storage disorder after Gaucher disease. It is an X-linked inborn error of the glycosphingolipid metabolic pathway. This results in accumulation of globotriaosylceramide (Gb3) within lysosomes in a wide variety of cells, thereby leading to the protean manifestations of the disease [1].

This topic provides an overview of Fabry disease, with an emphasis on kidney disease. The cardiac and neurologic manifestations, and the treatment of Fabry disease, are discussed elsewhere. (See "Clinical features, diagnosis, and management of patients with Fabry disease with cardiac disease" and "Neurologic manifestations of Fabry disease" and "Treatment of Fabry disease".)

EPIDEMIOLOGY — The prevalence of Fabry disease is estimated to range from 1:17,000 to 1:117,000 males in Caucasian populations [2-4]. However, the disease is seen across all ethnic and racial groups [4].

The prevalence of Fabry disease is probably underestimated given incomplete ascertainment. This is likely since [4,5]:

- The manifestations of the disease are nonspecific.
- The diagnosis is often not considered by physicians, given the rarity of the disease.
- The wrong diagnosis is often made initially. As an example, in the 366 European patients with Fabry disease participating in the Fabry Outcome Survey, the mean delay to correct diagnosis after symptom onset was estimated to be 13.7 and 16.3 years for males and females, respectively [5].

Fabry disease as a cause of ESRD — Renal manifestations occur in approximately 50 percent of affected patients by the age of 35 years, and the incidence increases significantly with age. A significant fraction of patients eventually develops end-stage renal disease (ESRD). As an example, all male patients in one study who survived to the age of 55 years developed ESRD [2]. However, in a registry of over 2000 patients with Fabry disease (mean age 37 to 40 years), the prevalence of ESRD was much lower (14 percent in men and 2 percent in women) [6]. By age 55 years, only 32 percent of men and 19 percent of women developed renal events, which ranged from new onset chronic kidney disease (defined as a glomerular filtration rate less than 60 mL/min/1.73 m2) to end-stage renal disease.

The prevalence of Fabry disease in dialysis populations has been examined in several screening studies. Random screening has identified fewer than 1 percent of hemodialysis patients as having Fabry disease, most of whom were already known to have the disease [7-13]. The following findings from different regions are illustrative:

- According to the 2010 annual data report by United States Renal Data System, Fabry disease accounted for only 95 new cases of ESRD between 2005 and 2009 (including 80 males and 15 females), which represents approximately 0.02 percent of the incident patients each year [7].
- In a Japanese study, six of 514 (1.2 percent) consecutive males on dialysis had low leukocyte alpha-Gal A levels, and were found to have a gene mutation [8]. Another Japanese study of 696 consecutive patients (295 females) found only four males and one female (0.7 percent) to have Fabry disease, and three were already known to have it [11].

- In a nationwide screen of the Austrian dialysis population, 85 of 2480 patients (3.4 percent, similar proportions in male and female) had a positive blood spot test with low alpha-Gal A levels [9]. Among these patients, only 5 women and 10 men had confirmed low leukocyte alpha-Gal A levels, representing 0.5 percent of the screened population. Only four males (0.16 percent) had the gene mutation, three of whom were already diagnosed.

A voluntary Fabry disease registry has been established to better understand the epidemiology and prognosis of the disease (www.lsdregistry.net/fabryregistry or 1-800-745-4447).

PATHOPHYSIOLOGY — The metabolic defect in Fabry disease is deficiency of the lysosomal hydrolase alpha-galactosidase A (alpha-Gal A), which catalyzes the hydrolytic cleavage of the terminal galactose from globotriaosylceramide (Gb3) [14]. The alpha-Gal A protein is encoded by a 12-kb gene mapped to the long arm (Xq22.1 region) of the X chromosome [15]. Several hundred mutations in the alpha-Gal A gene have thus far been identified [16,17]. Most kindreds have specific, or private, mutations, and de novo mutations are rare [18].

Gb3 is an intermediate in the degradative pathway of globoside. Globoside, a major glycosphingolipid in the red cell membrane and the kidney, is composed of ceramide attached to three sugar residues and an N-acetylgalactosamine residue (ceramide-Glc-Gal-Gal-GalNAc). Globoside is metabolized in lysosomes, particularly in the spleen, liver, and bone marrow. In the absence of significant alpha-Gal A activity, Gb3 accumulates in various cells and tissues. Tissue accumulation of Gb3 is inversely correlated with residual alpha-Gal A activity in leukocytes [2].

The accumulation of Gb3 is particularly prominent in the vascular endothelium (at levels up to 460-fold higher than normal), vascular smooth muscle cells, and pericytes [2,19,20]. The deposition of glycosphingolipid in these cells may lead to vascular occlusion, ischemia, and infarction. However, it is possible that accumulation of Gb3 in other cell types within the vessel wall may be important. As an illustrative example, enzyme replacement therapy in adults clears Gb3 from the endothelium but not from the rest of the vessel, and does not reduce the incidence of stroke [21].

Accumulation of Gb3 in autonomic ganglia, dorsal root ganglia, renal glomerular, tubular and interstitial cells, cardiac muscle cells, vascular smooth muscle cells, valvular fibrocytes, and cardiac conduction fibers may lead to the myriad other manifestations of the disease. Accumulation in the cornea also occurs, but is clinically silent. The actual clinical involvement varies significantly among different organs, which likely represents various rates of sphingolipid metabolism in different tissues [22].

Gb3 deposition may be only partially responsible for the manifestations of the disease. Other as yet unexplained factors might also contribute, since disease manifestations may be present in the absence of severe deposits. In one report of 57 symptomatic female patients with confirmed Fabry genotype who underwent a skin biopsy, only one patient had visible glycolipid accumulation in endothelial cells by light microscopy, and 10 to 50 percent had mild accumulation in other cell types [23]. However, cardiac, renal or cerebrovascular abnormalities were documented in 90 percent. Electron microscopy and examination of other organs such as kidney or heart were not done in this study.

Pathophysiology of renal disease — Gb3 accumulation in the kidney is inversely correlated with residual alpha-Gal A activity in leukocytes [2]. In addition, the magnitude of renal Gb3 content correlates positively with the severity of renal pathologic changes and inversely with kidney function. Thus, accumulation of Gb3 in the kidney is probably responsible for the renal manifestations of the disease. (See 'Renal manifestations' below.)

Gb3 accumulation in the kidney occurs preferentially in the glomeruli (especially podocytes, but also in endothelial, and mesangial cells), and in the distal tubule. The predilection for these two locations may explain the early renal manifestations of proteinuria and polyuria. In children with Fabry disease, for example, podocyte Gb3 accumulation was strongly associated with foot process width and the degree of proteinuria, implicating glomerular involvement in the early onset proteinuria observed in this disease [24].

The pathophysiology underlying the formation of renal sinus cysts, another manifestation in patients with Fabry disease, is unknown. (See 'Renal sinus cysts' below.) The presence of cysts is not related to residual alpha-Gal A activity, renal function, or level of proteinuria. It is unclear whether the cysts contain Gb3, or whether this is due to lymphatic overload or other processes.

CLINICAL PRESENTATION — Although variability exists, the symptoms of Fabry disease tend to appear in a predictable order in classically affected males (table 1) [18,20,25].

Overview of clinical manifestations — Clinical manifestations begin in childhood or adolescence, and include [2,5,20]:

- Severe neuropathic or limb pain, which may be precipitated by stress, extremes of heat or cold, and physical exertion. Neuropathic symptoms occur in more than 75 percent of patients with a mean age of onset of 10 years. (See "Neurologic manifestations of Fabry disease".)
- Telangiectasias and angiokeratomas, the latter commonly in groin, hip and periumbilical areas, are characteristic (picture 1 and picture 2). Thickening of the lips and bulbous nose have also been described. Dermatologic manifestations of Fabry disease occur in more than 70 percent of patients with a mean age of onset of 17 years.
- Renal manifestations such as proteinuria, polyuria, and polydipsia or otherwise unexplained renal insufficiency are common. Renal disease, particularly proteinuria, occurs in more than 80 percent of patients with a mean age of diagnosis of 35 to 40 years. (See 'Renal manifestations' below.)
- Other nonspecific manifestations, which tend to worsen in early adulthood, include heat, cold, and exercise intolerance, hypohidrosis (or hyperhidrosis [26,27]), lymphadenopathy, and gastrointestinal symptoms such as abdominal pain and diarrhea. These manifestations occur in 50 to 70 percent of patients, often by the fourth decade.

In adulthood, there is progressive cardiac and cerebral involvement, which accounts for the majority of deaths associated with Fabry disease [28]:

- Cardiac involvement includes concentric left ventricular hypertrophy, heart failure, coronary artery disease, aortic and mitral valve abnormalities, and conduction abnormalities. Cardiac manifestations occur in more than 80 percent of patients with Fabry disease, with a mean age of onset of 42 years. In some patients, these manifestations, particularly left ventricular hypertrophy, are the only recognized manifestations of the disease. Fabry disease is a potential cause of unexplained left ventricular hypertrophy. (See "Clinical features, diagnosis, and management of patients with Fabry disease with cardiac disease", section on 'Ventricular hypertrophy'.)
- Cerebrovascular involvement may lead to transient ischemic attacks and strokes, and can cause a wide range of neurologic symptoms, including blindness. In addition, enlargement of large cranial arteries (dolichoectasia) may occur. Transient ischemic attacks and strokes occur in approximately 25 percent of patients with a mean age of onset of 40 years. (See "Neurologic manifestations of Fabry disease".)

The age of symptom onset is more consistent in male hemizygotes than in female heterozygotes; approximately 80 percent of males have neurologic, dermatologic and cardiac manifestations by the second, third and fifth decades of life, respectively [5]. Males with atypical variants may present even later in life, diagnosed during evaluations for cardiomegaly or proteinuria [18].

Clinical manifestations in heterozygous females vary widely from no apparent clinical disease to full expression of the disease, possibly related to random X-chromosome inactivation, although this is not proven [29,30]. Up to 90 percent may have clinical manifestations [23].

Renal manifestations — Renal manifestations occur in at least 50 percent of male patients and about 20 percent of female patients [1,6]. When patients with Fabry disease present with renal manifestations, the principal findings are proteinuria and progressive renal insufficiency. Uncommonly, patients complain of polyuria and polydipsia, or are discovered by the presence of renal sinus cysts on an imaging study.

Proteinuria — Proteinuria, which may be tubular or glomerular in origin, may begin in the early teen years, but more typically appears during early adulthood. As an example, a long-term natural history study from the National Institutes of Health (NIH) reported proteinuria among 66 of 78 (85 percent) male patients with renal disease, with the average age of onset being 34 years (range 14 to 55) [2]. Nephrotic-range proteinuria was uncommon (18 percent of those with renal disease), and only a fourth of them developed nephrotic syndrome. However, among those with progressive kidney failure, 80 percent had nephrotic proteinuria.

Adult males with Fabry disease who have the highest levels of proteinuria (urine protein/creatinine ratio [UP/Cr] >1.5 gm/gm) also have the fastest decline in kidney function [31,32]. However, proteinuria is much less closely associated with renal function decline in adult female Fabry patients [31,32]. Thus, the concept that proteinuria per se is a direct promoter of progression in Fabry disease may be incorrect.

In addition to protein, the urine may contain oval fat bodies (tubular epithelial cells with lipid inclusions) with a lamellar structure and a Maltese cross pattern under polarized urine microscopy. (See "Urinalysis in the diagnosis of kidney disease", section on 'The assessment of lipiduria'.)

Chronic kidney disease — In untreated patients with Fabry disease, progressive CKD develops over time, sometimes resulting in ESRD. In the previously described natural history study from the NIH, the following findings were reported [2]:

- Forty-eight percent developed CKD (defined as a serum creatinine concentration ≥1.5 mg/dL [133 µmol/L]), which occurred at a median age of 42 years. In those with the lowest enzyme activity, CKD developed at an earlier mean age (22 versus 47 years).
- Twenty-four patients overall (29 percent), and all who survived to the age of 55 years, eventually developed ESRD (median age 47 years). Progression to ESRD from the diagnosis of CKD occurred over an average of four years (range 1 to 13), corresponding to a mean rate of decline in glomerular filtration rate (GFR) of 12 mL/min per 1.73 m2 per year. Once CKD developed, the rate of progression to ESRD did not vary with age.

Similar findings with respect to CKD and ESRD were reported in an English cohort study of 98 hemizygous males [20]. Eighty-four percent had proteinuria and 47 percent had decreased kidney function. However, the 31 percent of patients who developed ESRD did so at a younger age than in the study from the United States, with a mean age of dialysis initiation of 37 years; the youngest presented at 18 years of age.

However, other studies have reported a much lower incidence of ESRD among older individuals [6]. In a registry of over 2000 patients with Fabry disease (mean age 37 to 40 years), only 32 percent of men and 19 percent of women who were 55 years of age or older developed renal events, which ranged from new onset chronic kidney disease (defined as a glomerular filtration rate less than 60 mL/min/1.73 m2) to end-stage renal disease.

Although there are some conflicting observations in females, increased proteinuria in male patients with Fabry disease appears to correlate with an increased risk of progression to ESRD [2,31-35].

The effect of enzyme replacement therapy on the progression incidence and progression of CKD is discussed elsewhere. (See "Treatment of Fabry disease".)

Isosthenuria and Fanconi syndrome — Relative to other segments, the distal tubules are preferentially affected, leading to decreased urinary concentrating ability [36] and polyuria. Polyuria and polydipsia may be the earliest functional symptoms of Fabry renal disease [37]. Gb3 deposition in proximal tubules may also produce Fanconi syndrome, which includes the manifestations of proximal renal tubular acidosis. (See "Etiology and diagnosis of distal (type 1) and proximal (type 2) renal tubular acidosis".)

Renal sinus cysts — The prevalence of renal sinus and parapelvic cysts is increased in patients with Fabry disease relative to healthy controls [38,39]. As an example, in one study of 24 patients with Fabry disease and 19 age-matched healthy controls, 50 percent of Fabry patients compared with only 7 percent of controls had renal sinus cysts, respectively [38]. In contrast, simple cysts located in renal parenchyma are commonly found in the adult population [40]. Thus, the incidental discovery of multiple renal sinus cysts with an imaging study should raise the possibility of Fabry disease in the appropriate clinical setting.

Hypertension — In the NIH study, only 30 percent of 105 subjects developed hypertension, with over one-half developing increased blood pressure only after the onset of CKD [2]. Overall, the onset of CKD was followed by the development of hypertension, which was then closely followed by the onset of ESRD before death ensued.

INITIAL EVALUATION — Although this section will focus on the renal evaluation, most of the ensuing discussion is generally relevant to Fabry disease.

When to suspect Fabry disease — An evaluation for Fabry disease should be performed in males or females with the following clinical features suggestive of the diagnosis, particularly:

- Intermittent episodes of severe pain in the extremities (acroparesthesias)
- Cutaneous vascular lesions (angiokeratomas)
- Diminished perspiration (hypohidrosis)
- Left ventricular hypertrophy of unknown etiology in young adulthood
- Stroke of unknown etiology in young adulthood
- Chronic kidney disease of unknown etiology in young adulthood
- Multiple renal sinus cysts discovered incidentally

A family history suggestive of the disorder is particularly helpful. (See 'Clinical presentation' above and 'Renal manifestations' above.)

We also recommend an evaluation in the following patients:

- Females known or suspected to be carriers
- Some family members of newly diagnosed patients

Specific issues related to case finding in family members of patients with Fabry disease are presented below (see 'Evaluation of family members' below).

Initial assessment — An initial evaluation should consist of the following [18,25,30]:

- Detailed past medical history and review of systems. Clinical symptoms or signs such as neuropathic pain, heat intolerance (usually associated with exercise intolerance and avoidance of outdoors in summer months), decreased tear, saliva or sweat production, diarrhea, abdominal pain, angiokeratomas and foamy urine should be carefully documented at baseline. Any history of transient ischemic attacks or strokes (particularly involving the posterior circulation), and myocardial disease should be thoroughly explored.
- Detailed family history that focuses on relatives with unexplained neurologic disease or kidney failure that was transmitted as an X-linked trait. In the NIH series, family history contributed to the diagnosis in 46 percent of patients.
- Careful physical examination, looking for angiokeratomas, telangiectasias, hypo- or anhydrosis, corneal opacity, edema, abnormal cardiac examination (evidence of left ventricular hypertrophy, arrhythmia). Asymptomatic characteristic corneal opacities (cornea verticillata) that do not affect visual acuity and retinal and conjunctival vascular tortuosity are present in almost all Fabry males [1]. Formal slit-lamp examination may be necessary to appreciate the corneal opacities.
- Examination of urine sediment and measurement of renal function. With renal involvement, there may be oval fat bodies (degenerating tubular epithelial cells with lipid inclusions) with a lamellar structure and a Maltese cross pattern under polarized microscopy (picture 3); this is similar to what may be seen with nephrotic range proteinuria of any cause. (See "Urinalysis in the diagnosis of kidney disease" and "Urinalysis in the diagnosis of kidney disease", section on 'The assessment of lipiduria'.)
- Electrocardiogram to evaluate for left ventricular hypertrophy and conduction defects.

DIAGNOSIS — In the setting of clearly established family history and classic phenotype, the diagnosis can usually be confirmed **in males** if there is low alpha-Gal A activity in leukocytes or plasma [2,41,42]. Analysis of plasma alpha-galactosidase may be less sensitive than assay of enzyme activity in leukocytes [43].

Mutation analysis of the alpha-Gal A gene is required to make the diagnosis **in female carriers** (unless the woman is an obligate heterozygote [ie, the father is known to have Fabry]), and in males and females with atypical presentations or marginal alpha-Gal A levels [18,30,44]. Rarely, the diagnosis is made by biopsy of the skin or kidney when other means of diagnosis are unavailable. On the other hand, patients may be incidentally discovered to have Fabry disease if a kidney biopsy is performed to evaluate chronic kidney disease.

Diagnosis in classically affected males — Measurement of leukocyte alpha-Gal A activity is the standard enzymatic test at most laboratories. The sensitivity and specificity of the alpha-Gal A assay using leukocytes approaches 100 percent in males, but the assay will identify less than 50 percent of female carriers. Based on the available knowledge, neither ESRD nor dialysis affects the enzyme assay.

Although different methods have been used to describe the results, enzymatic activity level is most often expressed as the percent of normal [2]. The enzymatic level can vary by population tested:

- Alpha-Gal A activity in leukocytes is undetectable in over 50 percent of hemizygous males, and is usually less than four percent of normal control levels in the remainder [2].
- Levels in female carriers range from normal to very low [37].
- Cardiac variants, a form of atypical disease, have one to ten percent of normal activity levels.

Diagnosis in females or males with atypical presentations — We recommend genetic testing in females and males with marginal levels of alpha-Gal A activity. Although not required for the diagnosis in most patients, genotyping is recommended for all Fabry families since this knowledge may be particularly relevant for future therapies utilizing synthetic chaperones [45]. Only one member of each affected family needs to be genotyped. Since more than 300 distinct mutations have thus far been identified, identification of a mutation in a new family requires essentially complete resequencing of the gene. Genetic analysis is only done at selected laboratories (refer to www.genetests.org) [30].

Tissue diagnosis in rare settings — In some cases, biopsy of skin or culture of skin fibroblasts may be helpful in establishing the diagnosis, but is usually done only if no other means of diagnosis are available. Skin biopsy can demonstrate the characteristic glycolipid deposits in a relatively non-invasive way.

Kidney biopsy may be helpful in establishing the diagnosis, but it is not typically necessary. The diagnosis is sometimes made by accident when a kidney biopsy is obtained to diagnose the cause of proteinuria and/or decreased kidney function [44,46]. A kidney biopsy may be of particular use when patients have nephrotic syndrome, gross hematuria, or other symptoms that require exclusion of other diagnoses. (See 'Renal pathology' below.)

Renal pathology — Kidney biopsy findings by light microscopy and electron microscopy are characteristic in Fabry disease, whereas immunofluorescence staining does not contribute to the diagnosis. Glycolipid accumulation is observed throughout the kidney:

- Light microscopy shows vacuolization of visceral glomerular epithelial cells (podocytes) and distal tubular epithelial cells [2]. This is consistent with the described pattern of glycolipid accumulation, with podocytes and distal tubular cells showing the largest amount. Smaller deposits in cells of the mesangium glomerular endothelium [22], proximal tubule (picture 4A-B) [22,47,48], and in the endothelium of peritubular capillaries and arteries may be difficult to appreciate by routine light microscopy.
- On electron microscopy, deposits of Gb3 appear within enlarged secondary lysosomes as lamellated membrane structures, called myeloid or zebra bodies (picture 5). These inclusions, composed of concentric layers with a periodicity of 3.5 to 5 nm and with an onion skin appearance, are considered a **hallmark** of glycolipid storage disorders [49]

The ultrastructural findings on kidney biopsy are highly characteristic and frequently point to the diagnosis. However, lamellar inclusions have been described in other conditions, including silicosis and gentamicin toxicity [50-53]. The location of the inclusions is sometimes helpful in making the distinction between these diseases. Lamellar inclusions associated with gentamicin occur in proximal tubules, whereas in Fabry disease, the inclusions are most striking in podocytes and distal tubules.

Nonspecific findings in patients with more advanced disease may include focal segmental and global glomerulosclerosis and tubulointerstitial fibrosis, with mesangial deposits staining for C3 and IgM [54]. Foam cells may also be seen but are not diagnostic of Fabry disease, as they may be seen in other lysosomal storage diseases (where lipid is in podocytes) and proteinuric states (where lipid is primarily in macrophages) [55].

Thus, renal Gb3 content is significantly higher, and glomerular and tubulointerstitial changes and kidney function worse, in patients with undetectable alpha-Gal A activity compared with those with greater than 1 percent of normal activity.

DIFFERENTIAL DIAGNOSIS — Fabry disease is often misdiagnosed, given its wide range of nonspecific clinical manifestations and relative rarity. It has recently been termed "The New Great Imposter" [56]. Because of its rarity, patients with Fabry disease are often initially diagnosed with some other condition. The most commonly considered initial diagnoses in patients with Fabry disease in the Fabry Outcome Survey were [4,5]:

- Rheumatologic conditions including dermatomyositis or rheumatic fever. However, the characteristic heliotrope rash and elevated serum muscle enzymes distinguish juvenile onset dermatomyositis from Fabry disease. In addition, the pain and dermatologic symptoms of acute rheumatic fever are typically self-limited, lasting less than a month. (See "Diagnosis of juvenile dermatomyositis and polymyositis" and "Clinical manifestations and diagnosis of acute rheumatic fever".)
- Arthritis. However, Fabry disease is not characterized by synovial inflammation. (See "Diagnosis and differential diagnosis of rheumatoid arthritis".)
- Neuropsychological disease. However, many common manifestations of Fabry, including proteinuria, left ventricular hypertrophy, and angiokeratomas, are not typical in patients with psychiatric disease. (See "Neurologic manifestations of Fabry disease".)
- Fibromyalgia. As above, many common manifestations of Fabry, including proteinuria, left ventricular hypertrophy, and angiokeratomas, are not common in patients with fibromyalgia. (See "Clinical manifestations and diagnosis of fibromyalgia in adults".)
- Erythromelalgia. However, patients with Fabry disease do not have thrombocythemia, which can cause pain in the extremities of patients with polycythemia vera and essential thrombocythemia. (See "Clinical manifestations and diagnosis of polycythemia vera", section on 'Erythromelalgia'.)
- Hereditary hemorrhagic telangiectasia. Although patients with Fabry disease may have telangiectasias, they do not typically develop spontaneous epistaxis or gastrointestinal bleeding, as do patients with hereditary hemorrhagic telangiectasia. (See "Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)".)
- Meniere disease. Although tinnitus is present in nearly 40 percent of patients with Fabry disease, the presence of neuropathic pain, angiokeratomas, and proteinuria helps distinguish it from Meniere disease. (See "Meniere disease".)
- Multiple sclerosis. However, the presence of angiokeratomas, proteinuria, and left ventricular hypertrophy, which are not features of multiple sclerosis, provide clues to Fabry disease. (See "Clinical features of multiple sclerosis in adults".)
- Irritable colon. However, neuropathic pain, angiokeratomas, and proteinuria are not features of irritable bowel syndrome. (See "Irritable bowel syndrome in patients with inflammatory bowel disease".)
- Idiopathic hypertrophic cardiomyopathy. Echocardiography may be able to distinguish patients with Fabry disease from those with other causes of left ventricular hypertrophy. (See "Clinical features, diagnosis, and management of patients with Fabry disease with cardiac disease".)
- Kidney failure of unknown etiology. When occurring in a young individual, kidney disease of unknown etiology should prompt an evaluation for Fabry disease, particularly other common manifestations (eg, neuropathic pain) and a family history of kidney failure are present. (See 'When to suspect Fabry disease' above.)

As a result, the diagnosis of Fabry disease in patients without a known family history of the disorder is usually made by specialists and subspecialists: dermatologists (28 percent); neurologists (23 percent); nephrologists (19 percent); rheumatologists (2 percent); and cardiologists (2 percent) [2]. Consideration of Fabry disease as a possibility is the major hurdle to making the correct diagnosis in such patients.

FOLLOW-UP ASSESSMENT — Once diagnosed, patients with Fabry disease, or asymptomatic carriers, should be followed closely using an interdisciplinary approach that involves routine care by nephrology, cardiology, and neurology, with input from dermatology and ophthalmology as required [18,57]:

- Annual reevaluation with documentation of any clinical symptoms or signs. The annual exams should also include routine hematology and chemistry profiles, urinalysis, urinary protein to creatinine ratio or albumin to creatinine ratio, and an estimation of renal function such as estimated glomerular filtration rate or measurement of the creatinine clearance. (See "Assessment of kidney function" and "Calculation of the creatinine clearance".)
- Echocardiography and electrocardiography to detect or monitor cardiac abnormalities at least every two years.
- Asymptomatic female carriers should also have a complete baseline evaluation as above and should be reevaluated every three to five years, with increasing frequency with age. Atypical males with Fabry disease should be evaluated and monitored annually similar to those classically affected.

EVALUATION OF FAMILY MEMBERS — In families known to have Fabry disease, we suggest the following approach in individuals at risk [30]:

- At risk or symptomatic male relatives of an affected individual. These males should be screened with an enzymatic assay (blood or leukocyte), even if asymptomatic. If deficient alpha-Gal A activity is found, the individual should undergo comprehensive genetic analysis to identify the lesion, unless the mutation has been identified in the affected relative. (See 'Diagnosis in females or males with atypical presentations' above.)
- At risk female relatives of an affected individual, a female with a family history of Fabry disease, or a female with symptoms suggestive of Fabry disease. When testing women, the high false negative rate of alpha-Gal A testing in female carriers must be recognized [18,44]. Given the high variability of enzyme activity level in women, genetic testing of women with normal alpha-Gal A levels should be strongly considered.

Although available, routine prenatal screening is **not** recommended, as there are no data to suggest efficacy of initiating enzyme replacement therapy during infancy [30]. Prenatal testing involves measuring alpha-Gal A activity in fetal cells obtained through amniocentesis or chorionic villous sampling; the latter allows earlier (9 weeks versus 16 weeks) and faster test results (hours versus 2 weeks). However, a genetic mutation analysis must also be done because the sample may be contaminated with maternal tissue or female fetuses may have variable residual enzymatic activity.

Some have advocated screening by testing for elevated urinary excretion of Gb3. Mass spectrometry is one available method, with abnormally high levels being relative to healthy controls tested in the same lab [58,59]. However, urine Gb3 may not always be elevated in heterozygotes and remains a suboptimal marker of Fabry disease. We do not advocate its use either for screening or monitoring treatment response. Screening by testing for urinary lyso-Gb3, rather than Gb3, may prove more promising as a diagnostic and disease severity indicator [60].

SUMMARY AND RECOMMENDATIONS

- Fabry disease, also called Anderson-Fabry disease, is the second most prevalent lysosomal storage disorder after Gaucher disease. It is an X-linked inborn error of the glycosphingolipid metabolic pathway. The metabolic defect in Fabry disease is deficiency or defect in the lysosomal hydrolase alpha-galactosidase A (alpha-Gal A), which catalyzes the hydrolytic cleavage of the terminal galactose from globotriaosylceramide (Gb3). This results in accumulation of Gb3 within lysosomes in a wide variety of cells, such as vascular endothelium, autonomic and dorsal root ganglia, renal glomerular, tubular and interstitial cells, cardiac muscle cells, vascular smooth muscle cells, valvular fibrocytes, and cardiac conduction fibers. Accumulation of Gb3 in these cells may produce the many manifestations of the disease. (See 'Introduction' above and 'Pathophysiology' above.)
- The prevalence of Fabry disease is estimated to range from 1:17,000 to 1:117,000 males in Caucasian populations, although the disease is seen across all ethnic and racial groups. The prevalence of Fabry disease is probably underestimated given incomplete ascertainment due, in part, to the nonspecific manifestations of the disease. (See 'Epidemiology' above.)

- Renal manifestations occur in approximately 50 percent of affected male patients by the age of 35 years, and the incidence increases significantly with age. A majority of male patients and a significant fraction of female patients eventually develop end-stage renal disease. Random screening has identified that 0.36 to 1.5 percent of hemodialysis patients have Fabry disease, many of whom were already known to have the disease. (See 'Fabry disease as a cause of ESRD' above.)
- Although variability exists, the symptoms of Fabry disease tend to appear in a predictable order, beginning in childhood or adolescence, in classically affected males (table 1) (see 'Overview of clinical manifestations' above):
    - Severe neuropathic or limb pain, which may be precipitated by stress, extremes of heat or cold, and physical exertion.
    - Telangiectasias and angiokeratomas, the latter commonly in groin, hip and periumbilical areas, are characteristic (picture 1 and picture 2). Thickening of the lips and bulbous nose have also been described.
    - Proteinuria, polyuria, and polydipsia or otherwise unexplained renal insufficiency.
    - Heat, cold, and exercise intolerance, hypohidrosis (or hyperhidrosis), lymphadenopathy, and gastrointestinal symptoms such as abdominal pain and diarrhea.
    - In adulthood, there is a high risk of progressive cardiac and cerebral involvement, especially in males.
- Approximately 80 percent of males have neurologic, dermatologic and cardiac manifestations by the second, third and fifth decades of life, respectively. Males with atypical variants may present even later in life, while clinical manifestations in heterozygous females vary widely from no apparent clinical disease to full expression of the disease, possibly related to random X-chromosome inactivation. (See 'Overview of clinical manifestations' above.)
- Renal manifestations occur in at least 50 percent of male patients and about 20 percent of female patients. When patients with Fabry disease present with renal manifestations, the principal findings are proteinuria and progressive renal insufficiency. Less commonly, patients complain of polyuria and polydipsia, or are discovered by the presence of renal sinus cysts on an imaging study. (See 'Renal manifestations' above.)
- Fabry disease should be suspected in males or females with the following features (See 'When to suspect Fabry disease' above.):
    - Intermittent episodes of severe pain in the extremities (acroparesthesias)
    - Cutaneous vascular lesions (angiokeratomas)
    - Diminished perspiration (hypohidrosis)
    - Left ventricular hypertrophy of unknown etiology in young adulthood
    - Stroke of unknown etiology in young adulthood
    - Chronic kidney disease of unknown etiology in young adulthood
    - Multiple renal sinus cysts discovered incidentally
- An initial evaluation should consist of a detailed medical history and physical examination looking for suggestive clinical symptoms, a family history of unexplained neurologic or kidney disease transmitted in an X-linked pattern, angiokeratomas, telangiectasias, hypohidrosis, corneal opacities, and an abnormal cardiac exam. Laboratory studies should include a urinalysis looking for proteinuria, an assessment of renal function, and an electrocardiogram. (See 'Initial assessment' above.)
- In the setting of clearly established family history and classic phenotype, the diagnosis is can usually be confirmed **in males** by a low alpha-Gal A activity in leukocytes or plasma. Mutation analysis of the alpha-Gal A gene is required to make the diagnosis **in female carriers** unless the woman is an obligate heterozygote (ie, the father is known to have Fabry), and in patients with atypical presentations or who have residual alpha-Gal A levels. (See 'Diagnosis' above.)

- The most commonly considered initial diagnoses in patients with Fabry disease were rheumatologic conditions or rheumatic fever. Other often-considered diagnoses include arthritis, neuropsychological disease, fibromyalgia, dermatomyositis, erythromelalgia, hereditary hemorrhagic telangiectasia, Meniere disease, multiple sclerosis, irritable colon, idiopathic hypertrophic cardiomyopathy, and kidney failure of unknown etiology. (See 'Differential diagnosis' above.)
- Once diagnosed, patients with Fabry disease, or asymptomatic carriers, should be followed closely using an interdisciplinary approach that involves routine care by nephrology, cardiology, and neurology, with input from dermatology and ophthalmology as required. (See 'Follow-up assessment' above.)
- In families known to have Fabry disease, we suggest screening at risk or symptomatic male relatives of an affected individual, at risk female relatives of an affected individual, females with a family history of Fabry disease, and females with symptoms suggestive of Fabry disease. (See 'Evaluation of family members' above.)

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Topic 7195 Version 14.0

GRAPHICS

Clinical manifestations of Fabry disease

Childhood
Pain, numbness of fingers and toes
Telangiectasias on ears, conjunctiva
Blue-black angiomatous macules or papules
Edematous upper eyelids
Raynaud phenomenon
Ophthamologic abnormalities
Early adulthood
Extensive telangectasias, angiokeratomas
Albuminuria, hematuria, oval fat bodies in urine
Edema
Fever, heat collapse, anhidrosis
Lymphadenopathy
Isothermia
30-40 years of age
Cardiac disease: coronary conduction defects, mitral insufficiency
Renal insufficiency
Cerebrovascular attacks
Neurologic findings suggesting multiple sclerosis

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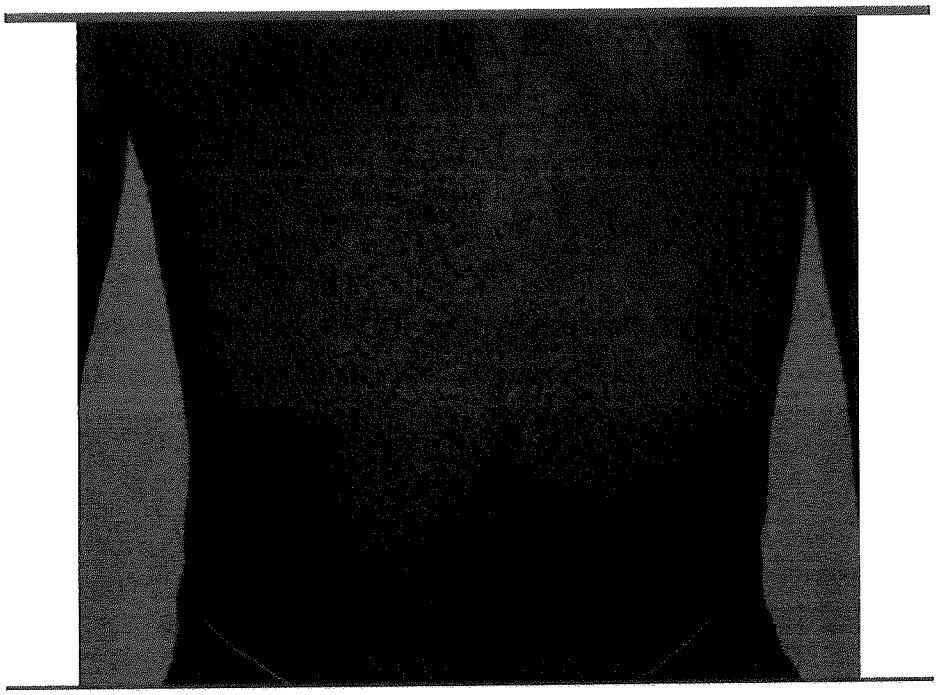
Graphic 57531 Version 3.0

Angiokeratomas are distributed in a typical symmetrical fashion on the torso



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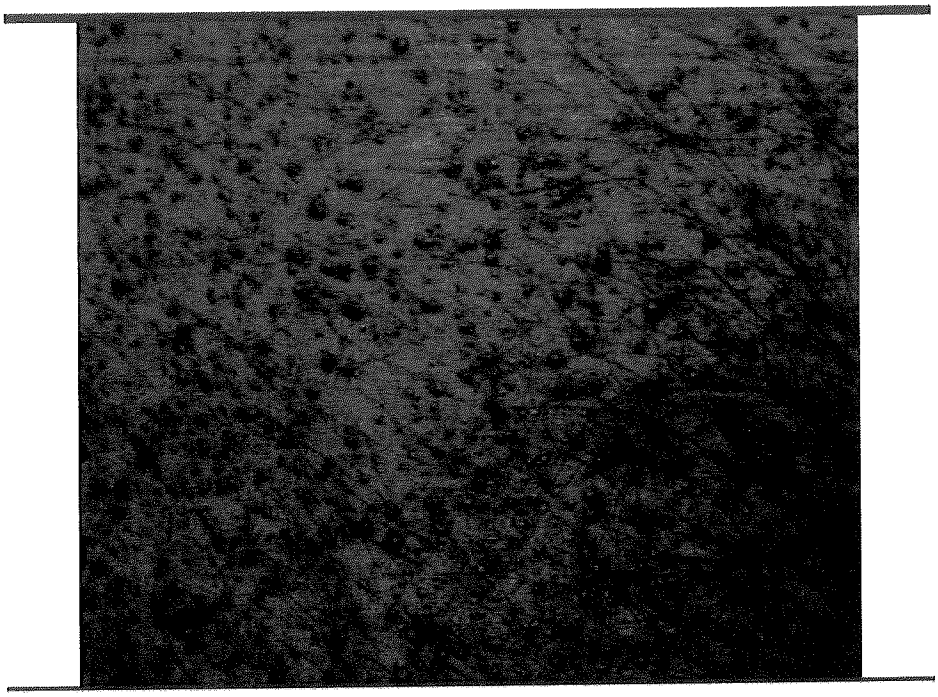
Graphic 81624 Version 2.0

Higher power view demonstrates the elevated papules



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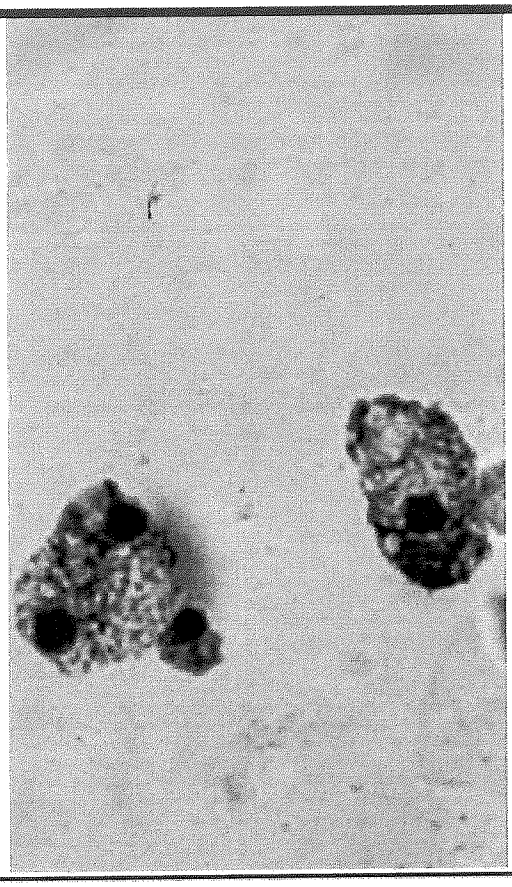
Graphic 71039 Version 2.0

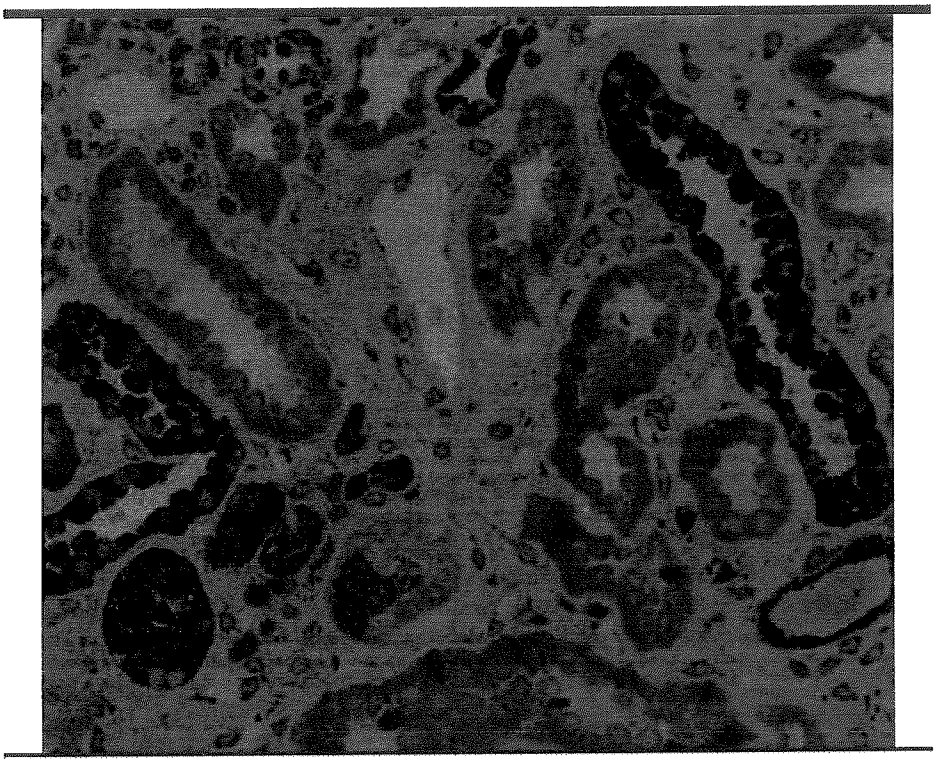
Vacuolated uroepithelial cells



Urine showing vacuolated urinary epithelial cells (oval fat bodies) in a Fabry patient (Papanicolaou stain, original magnification X160).

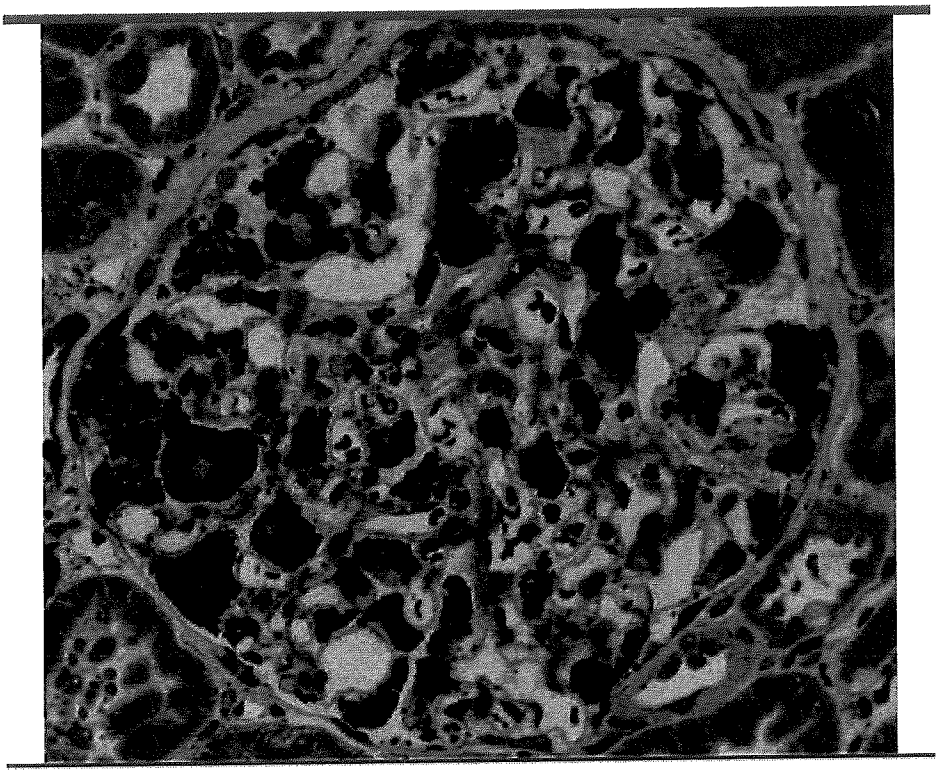
Graphic 54906 Version 6.0

Plastic embedded renal tissue demonstrating glycolipid inclusion bodies in distal tubules, with relative sparing of proximal tubules, and interstitial fibrosis (toluidine blue stain, original magnification X80)



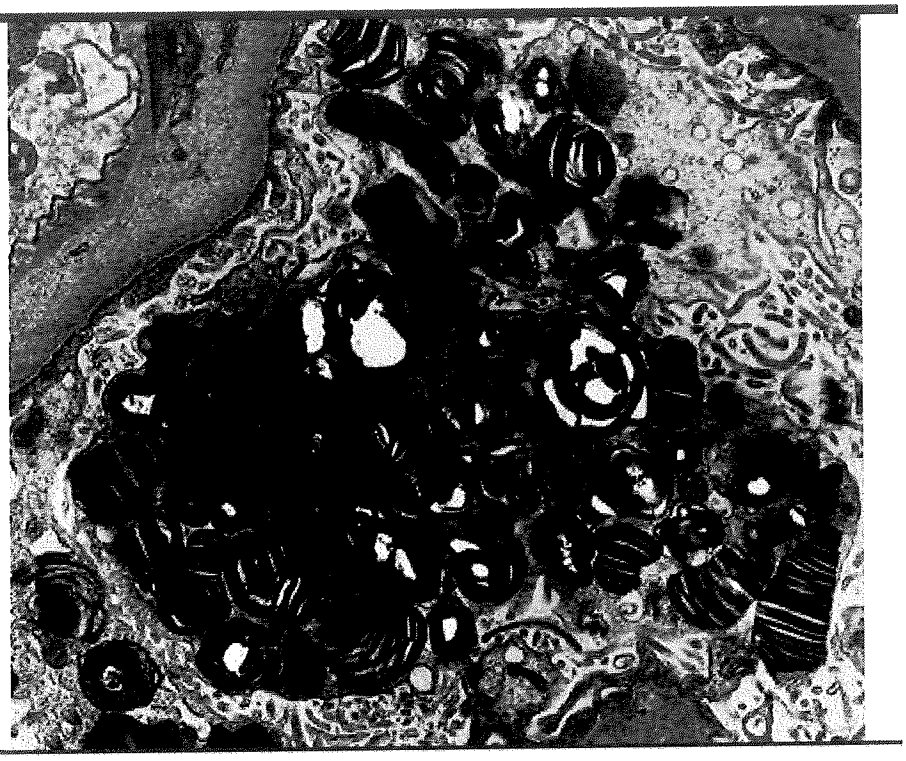
Graphic 54672 Version 6.0

Plastic embedded tissue showing in site deposition of glycolipid in glomerular podocytes (toluidine blue stain, original magnification X80)



Graphic 75690 Version 7.0

Electron micrograph showing lamellar osmophilic inclusions in a glomerular podocyte



The foot processes are intact. (Original magnification X20,000).

Graphic 68849 Version 7.0

Disclosures

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Conflict of interest policy

Patient information: Gout (Beyond the Basics)

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All topics are updated as new evidence becomes available and our peer review process is complete.
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GOUT OVERVIEW — Gout is a painful and potentially debilitating condition that develops in some people who have chronically high blood levels of urate (commonly referred to as uric acid). Not everyone with high blood urate levels (called hyperuricemia) develops gout; up to two-thirds of individuals with hyperuricemia never develop symptoms. It is unclear why some people with hyperuricemia develop gout while others do not, but the symptoms of gout result from the body's reaction to deposits of urate crystals in tissues.

Although the joints are the most commonly affected part of the body, urate crystals can form in the kidney or other parts of the urinary system, where they can occasionally impair kidney function or cause. Kidney stones caused by uric acid crystals occur in approximately 15 percent of people with gout. This compares with an 8 percent risk of kidney stones in people without gout.

Gout is different from another disease called calcium pyrophosphate crystal deposition disease (formerly called "pseudogout," which is discussed in a separate topic review). This develops in some people in response to the presence of a different type of crystal known as a calcium pyrophosphate (CPP) crystal. (See "Patient information: Pseudogout (Beyond the Basics)".)

GOUT RISK FACTORS — Gout usually develops in adulthood and is rare in children. It commonly develops earlier in adult men (often at ages 30 to 45 years) than in women (usually after age 55), and is particularly common in people older than 65 regardless of gender. It is estimated that gout affects nearly 4 percent of adults in the United States.

There are several medical conditions and lifestyle choices that increase the risk of developing gout, including:

- Obesity
- High blood pressure
- Chronic kidney disease
- Injury
- Fasting
- Consuming excessive amounts of alcohol (particularly beer, whiskey, gin, vodka, or rum) on a regular basis
- Overeating
- Consuming large amounts of meat, seafood, or beverages containing high fructose corn syrup (such as non-diet sodas)
- Taking medications that affect blood levels of urate (especially diuretics)

In people already diagnosed with gout, there are also certain characteristics that increase the risk of disease flares. These include:

- Injury or recent surgery
- Fasting
- Consuming excessive amounts of alcohol

- Overeating
- Taking medications that affect blood levels of urate

GOUT SYMPTOMS — Gout attacks (also called flares) are sudden episodes of severe joint pain, usually with redness, swelling, and tenderness of the joint. Although an attack typically affects a single joint, some people develop a few inflamed joints at the same time. The pain and inflammation usually reach their peak intensity within 12 to 24 hours and generally improve completely within a few days to several weeks, even if untreated. It is not clear how the body "turns off" a gout attack.

The characteristic pain and inflammation of gout develop when white blood cells and cells in the joint linings attempt to surround and digest urate crystal deposits. These cells recognize the crystal deposits as foreign material and release chemical signals that contribute to the pain, swelling, and redness associated with a gout attack.

PHASES OF GOUT — There are three main phases of gout: acute gouty arthritis, intercritical gout, and chronic tophaceous gout.

Acute gouty arthritis — Initial gout flares usually involve a single joint, most often the big toe or knee. This attack is known as acute gouty arthritis. Over time, the attacks can begin to involve multiple joints at once and may be accompanied by fever. People with osteoarthritis in the fingers may experience their first gout attacks in the fingers rather than the toes or knees.

Intercritical period — The time between gout attacks is known as an intercritical period. A second attack typically occurs within two years, and additional attacks may occur thereafter. If gout is untreated over a period of several years, the time between attacks may shorten, and attacks may become increasingly severe and prolonged.

Chronic tophaceous gout — People who have repeated attacks of gout or persistent hyperuricemia for many years can develop tophaceous gout. This designation describes the accumulation of large numbers of urate crystals in masses called tophi. People with this form of gout develop tophi in joints, bursae (the fluid-filled sacs that cushion and protect tissues), bones, and cartilage, or under the skin. Tophi may cause erosion of the bone and eventually joint damage and deformity.

The presence of tophi near the knuckles or small joints of the fingers can be a distressing cosmetic problem. Tophi are usually not painful or tender. However, they can become inflamed and can cause symptoms like those of an acute gouty attack (picture 1).

Tophaceous gout was more common in the past, when treatment for hyperuricemia was unavailable. Certain groups are still at risk for tophaceous gout, including:

- People who are treated with cyclosporine after organ transplantation
- Those who cannot tolerate or do not receive adequate doses of medications to treat hyperuricemia (for example, due to kidney failure or drug allergy)
- Women who are postmenopausal, especially those taking a diuretic

The risk factors listed previously for gout can also contribute to the development of tophaceous gout. (See 'Gout risk factors' above.)

GOUT COMPLICATIONS — People with gout are at increased risk of developing kidney stones. The kidney stones composed of uric acid that are part of gout often contain calcium crystals as well. The crystals can collect in the urinary tract and form a stone. If a stone is large enough, it can block one of the ureters (tubes that carry urine from the kidney to the bladder and out of the body) (figure 1). Medications that increase the amount of uric acid excreted by the kidneys may increase the risk of developing kidney stones.

GOUT DIAGNOSIS — There are many illnesses that can cause joint pain and inflammation. Gout is strongly suspected if a person has an acute attack of joint pain, followed by a period in which there are no symptoms. It is important to confirm the diagnosis of gout to ensure that potentially harmful medications are not taken unnecessarily over a prolonged period of time.

The best way to diagnose gout is to examine synovial fluid from an affected joint under a microscope to look for urate crystals in the sample. To obtain the fluid, the provider uses a needle and syringe to withdraw a small amount of fluid from inside the joint. Tophi located just beneath the skin can also be sampled with a needle to diagnose tophaceous gout.

However, some clinicians do not have the facilities to check for urate crystals in the synovial fluid when symptoms are present. In this case, the tentative diagnosis is based upon a person's symptoms and a physical examination. Criteria for suspecting gout include:

- Pain and inflammation initially involving one joint at a time, especially the joint at the base of the large toe
- Complete resolution of symptoms between attacks
- A blood test showing high levels of urate (most accurate for diagnosis after an acute flare resolves)

TREATMENT OF GOUT ATTACKS — The goal of treatment of flares of gouty arthritis is to reduce pain, inflammation, and disability quickly and safely. Deciding which medication to use is based upon several factors, including a person's risk of bleeding, kidney health, and whether there is a past history of an ulcer in the stomach or small intestine. Antiinflammatory medications are the best treatment for acute gout attacks and are best started early in the course of an attack.

People with a history of gout should keep medication on hand to treat an attack because early treatment is an important factor in determining how long it takes to decrease the pain, severity, and duration of an attack.

Nonsteroidal antiinflammatory drugs — Nonsteroidal antiinflammatory drugs (NSAIDs) work to reduce swelling in a joint and include ibuprofen (sample brand names: Advil, Motrin), naproxen (sample brand names: Aleve, Anaprox), indomethacin (brand name: Indocin), and celecoxib (brand name: Celebrex). Among the NSAIDs, naproxen is considered one of the safer medications with regard to cardiovascular side effects and has documented efficacy in acute gout. NSAIDs are generally recommended for people who have no history of kidney or liver disease, who have no bleeding problems, who do not use anticoagulant medications such as warfarin (Coumadin), and who have no history of a stomach or duodenal ulcer. (See "Patient information: Nonsteroidal antiinflammatory drugs (NSAIDs) (Beyond the Basics)".)

NSAIDs are most effective in the treatment of a gout attack when they are started as early as possible in the attack and at the higher doses of these agents—at which they have antiinflammatory, not just pain-relieving (analgesic), properties. People who have had previous attacks may start taking an NSAID at the first signs of a recurrence.

Although aspirin is an NSAID, it is not usually recommended for the treatment of gout because it can, depending upon the dose used, either raise or lower urate levels in the blood.

Colchicine — Colchicine may be prescribed instead of an NSAID. Colchicine does not increase the risk of ulcers, has no known interaction with anticoagulants, and, in proper doses, does not affect kidney function. However, colchicine can have bothersome side effects when given in excess, including diarrhea, nausea, vomiting, and crampy abdominal pain. Lower doses of colchicine than formerly used have been shown to be as effective for acute gout as the higher doses recommended in the past, and the gastrointestinal side effects have been much less of a problem. Colchicine seems to be most effective when given at the first symptoms of an acute attack. Colchicine should be taken only as a pill. People with impaired kidney function need even lower doses. The intravenous preparation of colchicine should be avoided because of potentially severe adverse effects.

Corticosteroids — Antiinflammatory steroids, also known more properly as glucocorticoids, are effective agents for treating acute gout flares. Commonly used oral corticosteroids include prednisone, prednisolone, and methylprednisolone.

Corticosteroids may be used if NSAIDs and colchicine cannot be used. They may be injected directly into the affected joint (called an intraarticular injection) or they can be given as pills or by intramuscular injection. People who have multiple affected joints or who cannot take NSAIDs or colchicine may be given oral steroids. There may be an increased risk of recurrent gout attack (called a rebound attack) in people who take oral corticosteroids for severe attacks. For this reason, corticosteroid dosing should be reduced slowly over a period of at least 10 to 14 days.

PROPHYLACTIC ANTIINFLAMMATORY GOUT THERAPY — Prophylactic antiinflammatory therapy aims to prevent or reduce the occurrence of acute flares of gouty arthritis. Colchicine is usually recommended as prophylactic therapy; it is taken daily at low doses to avoid gastrointestinal side effects. Colchicine reduces the frequency of acute gout attacks, particularly while starting drugs that lower urate levels.

Prophylactic colchicine is not usually used alone as a long-term (years) treatment but is a helpful bridge as a person progresses from an acute flare to urate-lowering therapy. Although not nearly as well-studied as colchicine, daily

nonsteroidal antiinflammatory drugs (NSAIDs) are sometimes used for prophylactic therapy and may have an advantage (because of pain relieving properties) for people who also have osteoarthritis.

LONG-TERM URATE-LOWERING THERAPY — Therapy to prevent progression of gout may include medications and lifestyle changes that can be used long-term to lower urate levels and thus to prevent or reverse the urate crystal deposits that cause worsening of gout. Progressive gout can cause bone destruction and deformity (gouty arthropathy), disability, kidney stone formation, and, possibly, kidney damage. People who have one or more of these complications are especially strongly encouraged to take a urate-lowering treatment.

Not everyone with gout will require urate-lowering therapy; those very fortunate few who have rare or mild attacks may be able to manage their gout by treating the acute attacks alone, but if progression to joint damage or tophus development occurs, even these individuals should receive urate-lowering medication. On the other hand, people with frequent gout flares or with flares that are unusually prolonged, painful, or disabling, or with gouty joint damage or tophi should always be encouraged to take urate-lowering therapy.

Medications — Urate-lowering (antihyperuricemic) medications lower urate levels in one of three ways: they increase uric acid elimination by the kidneys, they decrease production of urate, or they convert urate to the more readily excreted allantoin. Urate-lowering therapy is usually started after a gout attack has resolved. People who take their medication regularly and maintain urate levels below a goal-range of 6 milligrams/deciliter (mg/dL) over months to years eventually experience fewer attacks. At present, it is recommended that preventive therapy be continued indefinitely because there is no benefit to taking a break from medication.

- Probenecid increases the efficiency of uric acid excretion by the kidney and is called a uricosuric drug. Benzbromarone is a more potent uricosuric drug but is not available in the United States. Both drugs can cause side effects, including rash, upset stomach, and kidney stone formation. Effective probenecid use requires two or three doses daily. Probenecid is not effective in patients with advanced kidney disease.

- Losartan is used to treat high blood pressure but also has a useful, though weak, urate-lowering effect, as does the lipid-lowering drug fenofibrate. These agents can be useful adjuncts to urate-lowering treatment with allopurinol or febuxostat or with lifestyle modifications in gout patients with high blood pressure or high blood lipid levels, respectively.

- Allopurinol (brand names: Alloprim, Zyloprim) and febuxostat (brand name: Uloric) work by preventing the formation of uric acid. Allopurinol is the most commonly used drug for lowering urate levels in gout. Allopurinol can cause side effects, including rash, lowered white cell and platelet counts, diarrhea, and fever, although these problems occur in a small percentage of patients. The starting dose of allopurinol needs to be reduced in people with impaired kidney function, but doses can usually be gradually increased to achieve the target urate level. No such dose-lowering concern is present with febuxostat when used at the approved doses. Periodic measurement of liver function is recommended during treatment with febuxostat and with allopurinol.

- Pegloticase (brand name: Krystexxa) works by breaking down urate into allantoin, an end product that is more easily excreted. Pegloticase is given by repeated intravenous infusions and can lower urate levels rapidly and profoundly. This biological agent is expensive; may cause allergic-like infusion reactions, some of which can be severe; needs careful monitoring; and is effective in the long term in only about 50 percent of cases. For these reasons, it is recommended that pegloticase use be limited to patients with advanced gout that cannot be controlled with oral urate-lowering therapies.

Lowering urate levels to a goal range with oral medications is a process that should take a number weeks or months to achieve. During this period, doses of the uric acid-lowering medications should be gradually adjusted to meet the goal (usually a blood uric acid level <6 mg/dL). Very rapid urate lowering can cause more frequent acute flares of gout. Increased fluids are recommended during this time (at least two liters per day are recommended).

The antiinflammatory prophylactic therapy (colchicine or nonsteroidal antiinflammatory drugs [NSAIDs]) (see 'Prophylactic antiinflammatory gout therapy' above) can usually be safely discontinued when blood levels of urate are normal and have

been in the goal range for about six months. Longer prophylactic therapy may be needed in some patients, especially those with tophi. Blood levels of urate should be monitored periodically to ensure that the goal urate level is maintained.

Dietary changes — Changing your diet may reduce the frequency of gout attacks. Because obesity is a risk factor for gout, as well as for many other health conditions, losing weight is an important goal. However, starvation or fad diets are not recommended. (See "Patient information: Weight loss treatments (Beyond the Basics)".)

Diet guidelines for patients with gout have changed over time, and it is not completely clear which combination of foods is best.

You are encouraged to eat and drink:

- Low-fat dairy products
- Foods made with complex carbohydrates (whole grains, brown rice, oats, beans)
- Only a moderate amount of wine (up to two 5-ounce servings per day [about 300 mL per day] since this is not likely to increase the risk of a gout attack)
- Coffee (may decrease serum uric acid levels)
- Vitamin C (500 mg per day has a mild urate-lowering effect)

Changes in diet are often recommended along with medications. Diet change alone is unlikely to lower blood urate levels by more than about 15 percent, even if the diet is severely restricted. On the other hand, when diet control is accompanied by weight loss (often with increased exercise) improvements in urate control can be more impressive.

WHERE TO GET MORE INFORMATION — Your healthcare provider is the best source of information for questions and concerns related to your medical problem.

This article will be updated as needed on our web site (www.uptodate.com/patients). Related topics for patients, as well as selected articles written for healthcare professionals, are also available. Some of the most relevant are listed below.

Patient level information — UpToDate offers two types of patient education materials.

The Basics — The Basics patient education pieces answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials.

Patient information: Gout (The Basics)
Patient information: Calcium pyrophosphate deposition disease (pseudogout) (The Basics)
Patient information: Ganglion cyst (The Basics)

Beyond the Basics — Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are best for patients who want in-depth information and are comfortable with some medical jargon.

Patient information: Pseudogout (Beyond the Basics)
Patient information: Kidney stones in adults (Beyond the Basics)
Patient information: Nonsteroidal antiinflammatory drugs (NSAIDs) (Beyond the Basics)
Patient information: Weight loss treatments (Beyond the Basics)

Professional level information — Professional level articles are designed to keep doctors and other health professionals up-to-date on the latest medical findings. These articles are thorough, long, and complex, and they contain multiple references to the research on which they are based. Professional level articles are best for people who are comfortable with a lot of medical terminology and who want to read the same materials their doctors are reading.

Asymptomatic hyperuricemia
Clinical manifestations and diagnosis of gout
Diuretic-induced hyperuricemia and gout
Hyperuricemia and gout in renal transplant recipients
Pathophysiology of gouty arthritis

Prevention of recurrent gout
Treatment of acute gout

The following organizations also provide reliable health information.

- National Library of Medicine
  (www.nlm.nih.gov/medlineplus/healthtopics.html)
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
  (301) 496-8188
  (www.nih.gov/niams/)
- American College of Rheumatology
  (404) 633-3777
  (www.rheumatology.org)
- The Arthritis Foundation
  (800) 283-7800
  (www.arthritis.org)

[1,2]

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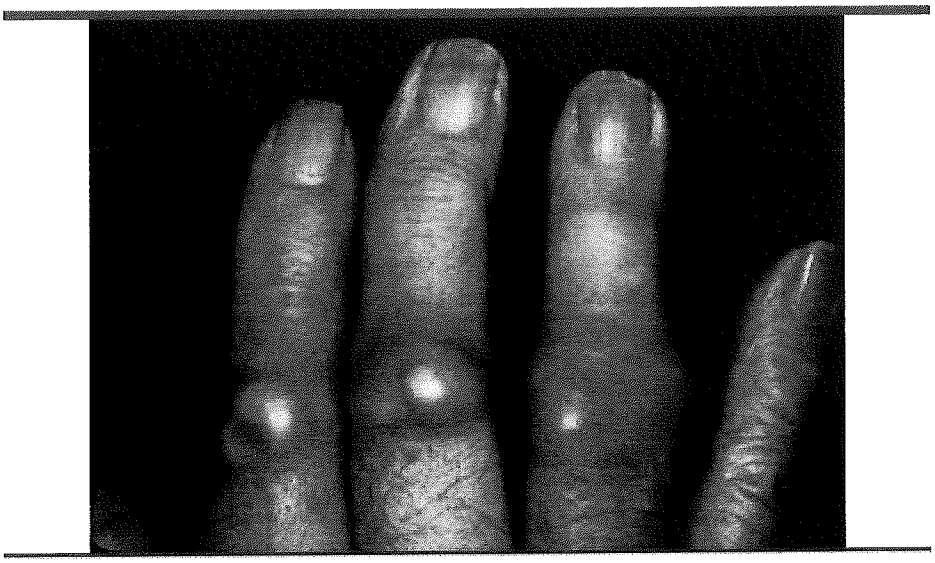
Topic 514 Version 13.0

GRAPHICS

Inflamed tophaceous gout

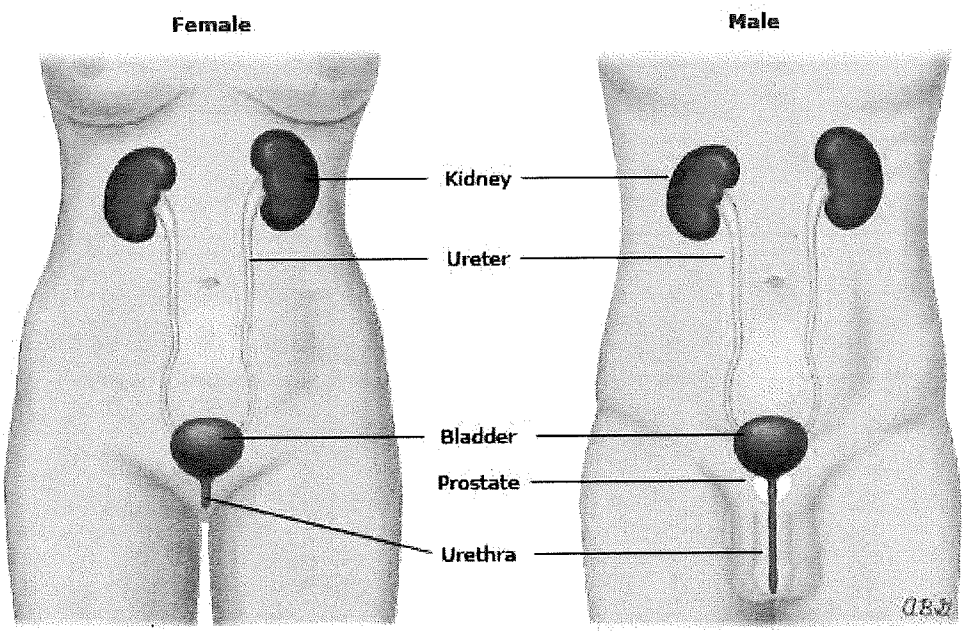


Three inflamed tophi over the proximal interphalangeal joints in a patient with chronic tophaceous gout. Several of the lesions ruptured spontaneously over the next three days, exuding a pasty material composed of urate crystals and inflammatory cells but no organisms. The inflammation largely subsided over one week after the administration of a nonsteroidal antiinflammatory drug.

Courtesy of Michael A Becker, MD.

Graphic 64367 Version 1.0

Anatomy of the urinary tract



Urine is made by the kidneys. It passes from the kidneys into the bladder through two tubes called the ureters. Then it leaves the bladder through another tube, called the urethra.

Graphic 79864 Version 6.0

Disclosures

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Conflict of interest policy

Adjuvant analgesics used for cancer pain

Category based on conventional use	Class	Subclass	Drugs
Multipurpose analgesics	Corticosteroids	-	Dexamethasone, prednisone, methylprednisone
	Antidepressants	Tricyclic	Amitriptyline, desipramine, nortriptyline
		SNRIs	Duloxetine, minalcipran, venlafaxine, desvenlafaxine
		SSRIs	Paroxetine, citalopram
		Other	Buproprion
	Alpha-2 adrenergic agonists	-	Tizanidine, clonidine
	Cannabinoids	-	Dronabinol, nabilone, others
	Topical analgesics	-	Local anesthetics capsaicin, tricyclic antidepressants, NSAIDs, others
Used for neuropathic pain	All multipurpose analgesics	See above	See above
	Anticonvulsants	-	Gabapentin, pregabalin, valproate, phenytoin, carbamazepine, oxcarbazepine, topiramate, lamotrigine, tiagabine
	Sodium channel blockers	Sodium channel modulator	Lacosamide
		Sodium channel blocker	Mexiletine, IV lidocaine
	N-methyl-D-aspartate receptor antagonists	-	Ketamine, memantine, dextromethorphan, amantadine
	GABA agonists	$GABA_a$ agonists	Clonazepam
		$GABA_b$ agonists	Baclofen
Used for bone pain	Osteoclast inhibitors	Bisphosphonates	Pamidronate, zolendronate, ibandronate
		-	Calcitonin
	Radiopharmaceuticals Plus: NSAIDs, corticosteroids	-	Strontium-89, samarium-153
Used for bowel obstruction	Anticholinergic drugs	-	Scopolamine, atropine, glycopyrrolate

	Somatostatin analogue Plus: Corticosteroids	-	Octreotide

GABA: gamma amino butyric acid.

Graphic 80423 Version 1.0

Therapeutic dose ranges for commonly used adjuvant analgesics

Category based on conventional use	Class	Drugs	Usual starting dose	Usual effective dose range*
Multipurpose analgesics	Corticosteroids	Dexamethasone	Varies	1-2 mg twice daily, orally or IV
		Prednisone	Varies	5-10 mg twice daily
	Antidepressants	Desipramine	10-25 mg at bedtime	50-150 mg at bedtime
		Duloxetine	20-30 mg daily	60-120 mg daily•
		Bupropion	75 mg twice daily	300-450 mg dailyΔ
		Venlafaxine, sustained release	75 mg once daily	150-225 mg daily
		Nortriptyline	10 to 25 mg at bedtime	50 to 150 mg at bedtime
	Alpha-2 adrenergic agonists	Tizanidine	1-2 mg at bedtime	2-8 mg twice daily
Used for neuropathic pain	Anticonvulsants	Gabapentin	100-300 mg twice daily	300-1200 mg three times daily
		Pregabalin	25-75 mg twice daily	150-300 mg twice daily
	GABA agonists	Clonazepam	0.5 mg at bedtime	0.5-3 mg daily
Used for bone pain	Osteoclast inhibitors	Pamidronate	-	60-90 mg monthly, IV
		Zoledronic acid	-	4 mg monthly, IV
Used for bowel obstruction	Anticholinergic drugs	Glycopyrrolate	0.1 mg daily	0.1-0.2 mg three times daily, subcutaneously
	Somatostatin analogue	Octreotide	Varies	0.1-0.3 mg twice daily, subcutaneously

GABA: gamma amino butyric acid.

* All dosages shown are for adult patients, oral administration, unless otherwise noted.

• Randomized trials conducted in patients with diabetic peripheral neuropathy suggest no additional efficacy from 120 mg daily versus 60 mg daily.

Δ Bupropion doses ≥150 mg should be sustained release.

Graphic 82318 Version 1.0

Comparison of representative glucocorticoid preparations

	Equivalent doses* (mg)	Relative antiinflammatory activity	Relative mineralocorticoid activity	Duration of action (hours)
Hydrocortisone (cortisol)	20	1	1	8 to 12
Cortisone acetate	25	0.8	0.8	8 to 12
Prednisone	5	4	0.8	12 to 36
Prednisolone	5	4	0.8	12 to 36
Methylprednisolone	4	5	0.5	12 to 36
Triamcinolone	4	5	0	12 to 36
Fludrocortisone	Not used for an antiinflammatory effect	10	125•	12 to 36
Dexamethasone	0.75	30	0	36 to 72

Prednisone and prednisolone are potent glucocorticoids and weak mineralocorticoids. Methylprednisolone and dexamethasone have no mineralocorticoid effect.

* Equivalent antiinflammatory dose shown is for oral or intravenous (IV) administration. Relative potency for intraarticular or intramuscular administration may vary considerably.

• Glucocorticoid doses which provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg fludrocortisone are prednisone or prednisolone 50 mg, or hydrocortisone 20 mg.

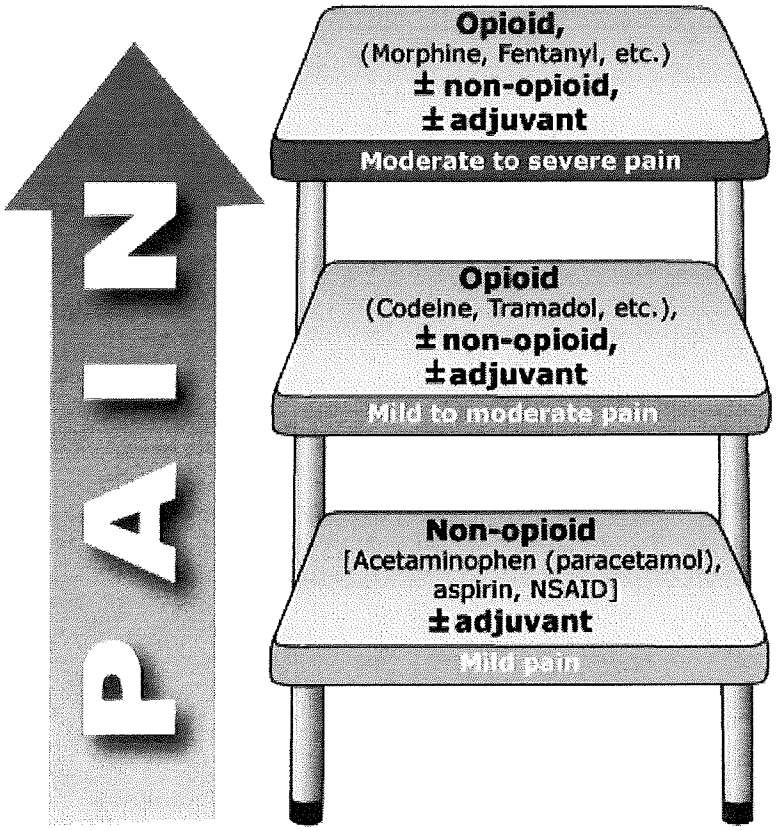
Data from:

1. *Schimmer BP, Parker KL. Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: The Pharmacological Basis of Therapeutics, 11th ed, Brunton LL, Lazo JS, Parker KL (Eds), McGraw Hill, NY. p.1587. Copyright © 2006.*
2. *Donohoue PA. The adrenal gland and its disorders. Kappy MS, Allen DB, Geffner ME (Eds), Charles C Thomas, Springfield, IL. p.403. Copyright © 2005 Charles C Thomas, Publisher, Ltd.*

Graphic 64138 Version 14.0

GRAPHICS

World Health Organization (WHO) analgesic ladder



Graphic 63298 Version 1.0

Epidemiology, clinical manifestations, diagnosis, and treatment of HIV-associated peripheral neuropathy

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INTRODUCTION — There are a number of distinctive neuropathic syndromes, which can be classified according to the timing of their appearance during HIV infection, their etiology, and whether they are primarily axonal or demyelinating. The most common of these is peripheral neuropathy, also referred to as distal symmetric peripheral neuropathy [1,2].

This topic will cover the pathogenesis, clinical manifestations, diagnosis, and treatment of distal symmetric peripheral neuropathy. The clinical manifestations of other HIV-associated neuropathies (eg, acquired inflammatory demyelinating polyradiculoneuropathy, cauda equina syndrome, diffuse infiltrative lymphocytosis syndrome (DILS), autonomic neuropathy, mononeuropathies, herpes zoster neuropathy, sensory ganglioneuritis) are discussed elsewhere. (See "Epidemiology, pathogenesis and clinical features of HIV-associated neuropathies".)

EPIDEMIOLOGY — The prevalence of distal symmetrical polyneuropathy (DSPN) in different series has varied from 9 to 63 percent [3-8]. This variability reflects differences in the degree of immunosuppression (higher prevalence with more advanced disease), in the definition of the neuropathy (symptomatic or asymptomatic), and in exposure to neurotoxic antiretrovirals [4,9,10]. Because of known neurotoxicities, didanosine and stavudine are no longer recommended for the treatment of HIV. (See "Selecting antiretroviral regimens for the treatment-naïve HIV-infected patient".)

Risk factors — In the era prior to potent antiretroviral therapy (ART), DSPN usually occurred in the setting of advanced immunosuppression [3,9,11-13]. In one report, for example, the mean CD4 count was 113/microL (range 26 to 275 cells/microL) [9].

In addition to immunosuppression, the level of HIV viremia was also correlated with the development of DSPN and the severity of symptoms [5,14,15]. In the Multicenter AIDS Cohort Study, the risk of DSPN was increased 2.3-fold in patients with an HIV RNA level >10,000 copies/mL at baseline [14].

However, in the era of potent ART, immunosuppression or high levels of viremia have not been associated with the development of DSPN in the vast majority of studies [5,6,8,16-18]. There are conflicting data on whether co-infection with hepatitis C is associated with DSPN [6,19].

Other factors associated with DSPN include aging, longer duration of HIV infection, host factors such as diabetes, hypertriglyceridemia [20], nutritional deficiencies, mitochondrial polymorphisms, substance use [21], and the use of older nucleoside reverse transcriptase inhibitors such as didanosine and stavudine [5,6,22-25]. In a large prospective study, 2141 HIV-infected patients were followed longitudinally for seven years with annual screening for symptoms and signs of peripheral neuropathy [25]. The risk of peripheral neuropathy was associated with aging and nucleoside analog use while sensory loss was associated with older age, nucleoside analog use and diabetes.

The role of certain antiretroviral medications is discussed below. (See 'Role of drugs' below.)

Effect of antiretroviral therapy on natural history — In most studies, the incidence of HIV-associated DSPN appears to have decreased in the era of potent ART compared with earlier cohorts, suggesting that effective suppression of HIV itself may have a beneficial effect on peripheral nerve function [5,7,15,16,26]. As an example, in a large cohort of 2515 HIV-infected patients, certain drugs (didanosine, stavudine, nevirapine, and certain protease inhibitors) were associated with the development of DSPN in the first year of use [5]. However, patients who did not develop DSPN in the first year of ART had a decreased risk of developing this complication with continued drug exposure. In another cohort of 2165 patients followed for

more than 3 years, incidence rates of peripheral neuropathy also declined with the initiation of ART [27]. These data suggest that immune restoration, or viral suppression of HIV, lead to a decreased risk of DSPN [5].

PATHOGENESIS — The pathogenesis of DSPN is incompletely understood and may be multifactorial. DSPN is termed a "dying-back" neuropathy to reflect the pattern of distal fiber loss [28]. It involves myelinated and unmyelinated axons of all sizes; this pattern of axon loss is indistinguishable from that seen with other toxic neuropathies.

There is a paucity of virus and associated inflammation in the peripheral nerves of patients with HIV [28]. Although there are some case reports of HIV being cultured from peripheral nerve, it is widely accepted that almost all recovered virus is from the resident macrophages and monocytes that migrate to areas of injury [28-32]. HIV itself may lead to local axonal injury through two separate mechanisms, both of which appear to be triggered by envelope protein gp120 [33]. One indirect route is via neuronal apoptosis; the other is through direct, local toxicity mediated through activation of mitochondrial caspases. Mitochondrial DNA damage has been shown to accumulate in distal mitochondria of long axons in HIV patients with DSPN, also supporting the possibility that distal mitochondrial dysfunction may play a role [34]. Likely more important, however, is the role that viral antigens play in provoking immune activation and inducing a microenvironment that is toxic to the peripheral nerve, as demonstrated by the following in vitro data:

- Immunohistochemical studies show macrophage and T cell infiltration of peripheral nerves and dorsal root ganglia [32,35].
- Activated cytokines are found in the dorsal root ganglia of HIV-infected patients with distal symmetrical polyneuropathy raising the possibility of a multifocal, immunologically mediated inflammatory disease [32].
- HIV gp120 activates Schwann cells via its chemokine receptor (CXCR4), leading both to neuronal apoptosis [33] and to production and release of tumor necrosis factor and other proinflammatory cytokines, which are directly toxic to neurons [36,37].
- HIV infection is associated with a reduction in mitochondrial DNA content and changes in morphology [38].

Not only does HIV infection result in nerve damage, but recent data suggests that reinnervation is impaired in patients with HIV infection, limiting the ability of the peripheral nervous system to heal itself [39].

Role of drugs — Many cases of distal symmetrical polyneuropathy are iatrogenic, due to intrinsic neuronal toxicities of certain antiretroviral medications [40-45]. The neuropathy is indistinguishable electrophysiologically from HIV-associated DSPN, although the hands may be affected more often in drug-induced cases [10,40-43]. The incidence of neuropathy is dose-dependent and increases with the duration of drug exposure [44]. The onset is typically seven to nine weeks after beginning therapy.

Dideoxynucleosides — The incidence of drug-related neuropathy has been shown to correlate directly with the degree of mitochondrial toxicity of particular nucleoside reverse transcriptase inhibitors, although a direct link between toxicity and oxidant stress has not been demonstrated [26,46-49]. Commonly implicated agents include stavudine (d4T) and to a lesser extent didanosine (ddI) [6,46].

The neurotoxicity of the combination of didanosine and stavudine was illustrated in a multicenter, randomized, partially double-blind trial of 620 antiretroviral-naive patients who were assigned to sequential three-drug regimens with different nucleoside analogues [50]. At a median of 2.3 years, symptomatic peripheral neuropathy was significantly more likely in patients treated with regimens containing didanosine and stavudine compared to those containing zidovudine and lamivudine (27 versus 10 percent) [50].

Genetic determinants may also play a role in risk in drug-induced DSPN:

- In a study of 509 HIV-infected patients, mitochondrial haplotype T was more common in those patients who developed DSPN [51]. Among 137 Caucasian subjects randomized to receive didanosine and stavudine, 21 percent of those who developed peripheral neuropathy belonged to mitochondrial haplogroup T compared to five percent of control subjects (odds ratio, 5.4).

- In a case-control study, hemochromatosis gene mutations were associated with a decreased risk of developing DSPN during dideoxynucleoside therapy [52]. This protective effect may be related to the requirement of iron for mitochondrial function.

The potential neurotoxicity of antiretroviral drugs does not preclude their use, since the beneficial effects on viral load suppression and immune function recovery appears to outweigh their potential neurotoxicity [4,5,16,17]. This apparent effect was illustrated in a report of 272 HIV-infected patients with CD4 counts less than 300 cells/microL who were followed for 30 months; the use of dideoxynucleosides did not increase the risk of peripheral neuropathy [4]. Similarly, dideoxynucleoside antiretroviral therapy was not a predictor of progression of distal sensory polyneuropathy in a cohort of 101 individuals with advanced HIV infection who were followed for 48 weeks [8].

Protease inhibitors — Some early data had suggested a potential role of protease inhibitors (PIs) in the pathogenesis of DSPN. One small study, which enrolled 101 patients with DSPN from 1998 to 2004, suggested an association with early generation protease inhibitors (ie, indinavir, saquinavir, and ritonavir) compared to later generation PIs [53]. The implications of these findings were unclear since most of these patients were also taking agents with known neurotoxicity, such as stavudine.

These findings prompted a much larger prospective, observational, multicenter study of current and past exposure to PIs as a risk factor for DSPN in 1159 HIV-infected patients [54]. Although PI use was associated with an increased risk of DSPN in the univariate analysis, this association disappeared after adjusting for previously validated concomitant risk factors, such as dideoxynucleoside use.

Furthermore, the clinical importance of these findings is less relevant now since none of these agents are used as first line agents for the treatment of HIV. (See "Selecting antiretroviral regimens for the treatment-naïve HIV-infected patient".)

Other drugs — Other drugs that can lead to the onset of DSPN include:

- Vincristine, which may be used to treat Kaposi's sarcoma
- Dapsone, which may be used to treat or prevent Pneumocystis jirovecii (formerly carinii) pneumonia
- Thalidomide, which may be used to treat aphthous ulcers
- Isoniazid and ethambutol, which are used to treat tuberculosis
- Nevirapine, a non-nucleoside reverse transcriptase inhibitor, used to treat HIV infection.

Host genetics — Human mitochondrial DNA sequences have diverged over time because of natural selection and human migration leading to distinct patterns of single nucleotide polymorphisms, called haplogroups [55]. Two studies in both non-Hispanic white [51] and non-Hispanic black patients [56] suggest that variations in these haplogroups may explain host susceptibility to mitochondrial drug injury.

CLINICAL MANIFESTATIONS — DSPN usually manifests as bilateral tingling, and numbness in the toes. The neuropathy gradually spreads proximally in the lower extremities, with only rare involvement of the upper extremities. The spread of sensory symptoms usually occurs over weeks to months. Neuropathic pain is common and may be the presenting symptom [57].

Neurologic examination shows sensory loss to all sensory modalities (vibration, pinprick, temperature) in a stocking distribution, while deep tendon reflexes are reduced or absent at the ankles and occasionally at the knees in more severe cases [4]. Distal weakness in the lower extremities can occur, although most patients have only sensory symptoms and signs. Sensory findings in the hands are more commonly associated with drug toxicity. HIV-related DSPN may evolve from painful to painless numbness.

The presence of brisk knee reflexes in patients with sensory loss raises the possibility of coexistent myelopathy, while the presence of proximal weakness or diffuse areflexia should prompt consideration of acquired inflammatory demyelinating

polyradiculoneuropathy, such as Guillain-Barre syndrome. (See "Clinical features and diagnosis of Guillain-Barré syndrome in adults".)

DIAGNOSIS — The diagnosis of peripheral neuropathy syndromes in HIV-infected patients is based mainly upon the clinical picture and physical examination.

Features that would prompt further evaluation, such as electromyography (EMG) and nerve conduction studies (NCS), may include significant weakness or asymmetry of signs. These findings may raise the possibility of alternative diagnoses (eg, acquired demyelinating polyradiculoneuropathy or vasculitic neuropathy). (See 'Other modalities' below.)

Laboratory testing — The evaluation of distal symmetrical polyneuropathy should include blood work to screen for other causes of this type of neuropathy. A typical panel would include:

- Hepatitis C antibody
- Vitamin B12 and folate levels
- Thyroid stimulating hormone assay
- Blood glucose
- Blood urea nitrogen and creatinine
- Serum protein electrophoresis and immunoelectrophoresis
- RPR

Although these laboratory tests are considered routine in the evaluation of DSPN, they are usually unremarkable in HIV-related or drug-induced polyneuropathy.

Other modalities — Other testing modalities include a subjective peripheral neuropathy screening test, electrodiagnostic studies, skin biopsy for epidermal nerve fiber density analysis, and nerve biopsy.

- Electrodiagnostic studies show a sensorimotor polyneuropathy, which is predominantly axonal [1]. Nerve conduction studies usually confirm a length-dependent axonal polyneuropathy, distinguishing DSPN from acquired inflammatory demyelinating neuropathy [1]. (See "Epidemiology, pathogenesis and clinical features of HIV-associated neuropathies".)

- Skin biopsy for epidermal nerve fiber density analysis has been shown to correlate with neuropathy severity, level of neuropathic pain, and sensory amplitudes on electrodiagnostic studies [58]. An abnormal skin biopsy predicts conversion to symptomatic DSPN in patients with no or asymptomatic neuropathy [59]. Skin biopsy can be positive, whereas electrodiagnostic studies may be negative, in patients with predominantly small nerve fiber involvement and thus can be a useful confirmatory test for early or predominantly small fiber DSPN.

- Nerve biopsy is not usually required but occasionally is performed in severe cases to exclude a confluent presentation of mononeuropathy multiplex. Biopsies show axonal loss with frequent foci of inflammation in the endoneurium or around perineurial blood vessels [29,40,42,60]. The severity of cases is judged clinically (eg, significant weakness on examination) and by electrodiagnostic tests (eg, significant axon loss). (See "Epidemiology, pathogenesis and clinical features of HIV-associated neuropathies".)

TREATMENT — Treatment options for HIV-related and drug-induced distal symmetrical polyneuropathy are limited.

Potential interventions — The effect of HAART on the severity of distal symmetrical polyneuropathy is unclear, although there is some evidence showing improved quantitative sensory measures in patients responding to HAART [60,61]. If a potentially neurotoxic drug is being used, such as stavudine (d4T), or didanosine (ddI), or thalidomide, it should be discontinued whenever possible. There may be a "coasting phenomenon" where the neuropathy worsens for one to six weeks following reduction in the dose of a nucleoside analog [40,42,43,62]. Gradual improvement then occurs; the time to recovery depends upon the dose and varies from 3 to 19 weeks [40,62].

The experimental agent recombinant human nerve growth factor has been shown to significantly improve pain compared to placebo, although this treatment does not improve neuropathy severity by examination, quantitative sensory testing, and

epidermal nerve fiber density. The presence of injection site pain in the treated cohort may have unblinded this study. This experimental agent is not approved by the United States Food and Drug Administration (FDA) [63,64].

Since dideoxynucleoside analogs are thought to cause peripheral neuropathy through the disruption of mitochondrial metabolism, there has been interest in using amino acid supplements needed for oxidative pathways. Although small, uncontrolled studies of acetyl L-carnitine suggested clinical benefit, [65,66] a controlled trial showed no benefit over placebo [67].

It is also important to address any nutritional or metabolic issues that may be contributing to DSPN.

Symptomatic approach — The medical management of HIV-associated DSPN is often by default based on studies of peripheral neuropathy in other disease states, such as diabetes. Management of polyneuropathy is thus largely symptomatic and is usually aimed at ameliorating the painful dysesthesias. The classes of drugs used include anticonvulsants, tricyclic antidepressants, topical analgesics, anti-inflammatories, and opioids for recalcitrant symptoms. (See "Overview of polyneuropathy".)

Abnormal processing of impulses from neuronal receptors contributes to neuropathic pain. Thus, a pharmacologic approach will include multiple possible targets with drugs of different classes, as discussed below. There are few data on the use of these agents in HIV-infected patients; most of the existing studies are small.

Anticonvulsants — Gabapentin is widely used in the treatment of neuropathic pain in diabetics and those with trigeminal neuralgia. A placebo-controlled trial in 26 HIV-infected patients with DSPN found gabapentin effective in reducing painful symptoms and sleep disturbance at four weeks of follow-up [68]. A large multicenter randomized controlled trial of pregabalin at maximally tolerated doses up to 1200 mg/day showed no benefit over placebo [69].

Two trials of lamotrigine in HIV neuropathy patients failed to show a clear benefit over placebo [70,71]

Antidepressants — Tricyclic antidepressants inhibit the reuptake of norepinephrine and serotonin into the presynaptic neurons and thereby block nociceptive receptors. The use of tricyclic antidepressants for HIV-associated DSPN is also based upon their efficacy in other conditions [72,73]. However, two double-blind trials in HIV-infected patients found that amitriptyline was no better than placebo [72,73].

Since these trials were small and had only short-term follow-up, many clinicians still use antidepressants in HIV-infected patients with DSPN based on their effectiveness in other populations. Options include amitriptyline or nortriptyline (starting at 10 mg at bedtime and increase as tolerated to 75 to 100 mg based on symptomatic improvement). Other potential agents include venlafaxine (37.5 to 225 mg/day) and duloxetine (60 mg/day).

Topical agents — Topical agents such as lidocaine or capsaicin (the active ingredient in hot chili peppers) are applied directly over the affected painful site. Capsaicin's mechanism of action may involve desensitization of peripheral endings of cutaneous afferent neurons. In a placebo-controlled trial of 307 HIV-infected patients with painful DSPN, an 8 percent capsaicin patch applied for 90 minutes reduced pain to a greater degree and in a greater proportion of patients than a low concentration capsaicin patch [74]. This patch is now commercially available. In contrast, capsaicin cream (0.075 percent) has been shown to be no better than placebo [75].

In a double-blind, placebo-controlled trial assessing the efficacy of lidocaine gel, lidocaine was safe but ineffective against symptoms of peripheral neuropathy [76].

Anti-inflammatory agents — Non-steroidal anti-inflammatory agents are not very effective for pain control and their chronic administration can be associated with adverse events, such as exacerbation of underlying renal disease secondary to HIV associated nephropathy.

Narcotic analgesics — Opioids, such as tramadol (50 to 100 mg three times daily), oxycodone morphine, or fentanyl patch may need to be added to the above mentioned therapies for breakthrough pain or to control recalcitrant symptoms. Dosage should be gradually titrated to alleviate symptoms. Chronic administration can lead to dependence and tolerance, which are predictable physiologic responses [77]. In contrast, addiction is defined as a long-term compulsive use of a substance in spite of harm. Clinicians need to be aware of this distinction when prescribing long-term use of narcotics.

Written patient-doctor contracts regarding opioid use are often helpful; referral to a pain specialist for evaluation is suggested [77].

Other — Small trials have demonstrated a benefit of smoked cannabis [78,79]. In one trial of 50 patients with HIV-associated DSPN, smoked cannabis reduced daily pain from DSPN by 34 percent compared with 17 percent with placebo cigarettes [78]. No serious adverse events were reported.

Acupuncture was no more efficacious than placebo in one study of 250 patients [73]. Mexiletine has also been evaluated in two studies but was ineffective in relieving symptoms [72,80].

The polypeptide, prosaptide, was ineffective in improving pain compared to placebo [81]. The NMDA antagonist, memantine, has also been shown to be ineffective compared to placebo [82].

SUMMARY AND RECOMMENDATIONS

- Distal symmetric polyneuropathy (DSPN) is the most common neurologic manifestation in HIV-infected patients. Risk factors for DSPN include advanced immunosuppression, level of HIV viremia, aging, diabetes, and nutritional deficiencies. (See 'Epidemiology' above.)
- Certain antiretroviral agents are associated with DSPN, including stavudine, didanosine, and nevirapine. (See 'Pathogenesis' above.)
- DSPN usually manifests as bilateral tingling, and numbness in the lower extremities. Neuropathic pain is common and may be the presenting symptom. Neurologic examination demonstrates sensory loss to all sensory modalities in a stocking distribution with reduced or absent deep tendon reflexes at the ankles. (See 'Clinical manifestations' above.)
- The diagnosis of peripheral neuropathy syndromes in HIV-infected patients is based upon the clinical picture and physical examination. (See 'Clinical manifestations' above.)
- Patients with features that suggest an alternative diagnosis, such as significant weakness or asymmetry of signs, should undergo electromyography (EMG) and nerve conduction studies (NCS). (See 'Diagnosis' above.)
- All patients who are being evaluated for DSPN should have laboratory testing for B12/folate, thyroid stimulating hormone assay, random glucose, creatinine, serum protein electrophoresis and immunoelectrophoresis, hepatitis C antibody, and RPR. (See 'Diagnosis' above.)
- Treatment options for HIV-related and drug-induced distal symmetrical polyneuropathy are limited. Antiretroviral agents that are associated with DSPN (eg, stavudine, didanosine, and nevirapine) should be discontinued. (See 'Treatment' above.)
- Management of DSPN is thus largely symptomatic and is usually aimed at ameliorating the painful dysesthesias. We suggest gabapentin for initial treatment (**Grade 2C**). If ineffective, we recommend choosing a second-line therapy based on a patient's comorbidities. Options include topiramate in patients with obesity or recurrent migraines, antidepressants, such as venlafaxine or duloxetine, for those with concomitant depression, and topical agents for those intolerant of systemic medications (**Grade 2C**).
- For breakthrough pain, topical capsaicin and opioid medications, such as tramadol, may be helpful. For recalcitrant symptoms, evaluation by a pain specialist and chronic opioid therapy may be considered.

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Cancer pain management: Adjuvant analgesics (coanalgesics)

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INTRODUCTION — Opioid therapy is the first-line approach for moderate or severe pain in populations with active cancer. However, the comprehensive management of pain in patients with cancer also requires expertise in the use of the nonopioid analgesics, such as acetaminophen (paracetamol), non-steroidal antiinflammatory agents (NSAIDs), and a group of drugs referred to as "adjuvant" analgesics or coanalgesics. Adjuvant analgesics are drugs that are marketed for indications other than pain, but are potentially useful as analgesics when added to opioid therapy in patients with chronic pain syndromes. (See "Cancer pain management with opioids: Optimizing analgesia" and "Cancer pain management: Use of acetaminophen and nonsteroidal antiinflammatory drugs".)

A stepwise approach to management of cancer pain that includes both opioid and nonopioid drugs has been codified in the World Health Organization's (WHO) "analgesic ladder" approach to cancer pain management (figure 1) [1]:

- Step 1, which represents mild to moderate cancer-related pain, suggests the use of acetaminophen or an NSAID, possibly combined with an adjuvant drug to provide additional analgesia, treat a side effect, or manage a coexisting symptom.
- For patients with moderate or severe pain, and those who do not achieve adequate relief with acetaminophen or an NSAID alone, treatment with a step 2 opioid (conventionally used for moderate pain) or a step 3 opioid (conventionally used for severe pain) is appropriate. On both steps 2 and 3, the use of an acetaminophen or an NSAID should be considered, as well as other drugs (adjuvants) to enhance analgesia or treat side effects.

The analgesic ladder approach is not an evidence-based guideline, but it provides a framework for the stepwise and systematic approach to managing cancer pain. (See "Cancer pain management: General principles and risk management for patients receiving opioids", section on 'General principles of pain management'.)

This topic review will cover the use of adjuvant analgesics in cancer pain management. Assessment of cancer pain, a review of specific cancer pain syndromes, the clinical use and side effects of opioid analgesics, use of acetaminophen and NSAIDs in patients with cancer pain, and non-pharmacologic methods of cancer pain management are covered elsewhere. (See appropriate topic reviews.)

DEFINITION OF AN ANALGESIC ADJUVANT — The term "adjuvant analgesic" was originally coined to refer to a small number of drugs that were marketed for indications other than pain, but were found to be potentially useful as analgesics in patients receiving opioid therapy. Over the past three decades, the number, diversity and uses of these drugs have increased dramatically, and several are now indicated as first-line therapy for certain types of pain [2]. As a result, the term "adjuvant analgesic" has become somewhat of a misnomer, but it is still commonly applied in the context of cancer pain. The term is used interchangeably with the term "coanalgesic".

Integration into cancer pain management — Adjuvant analgesics are often considered for treatment of chronic cancer pain when a patient is poorly responsive to opioids (ie, inability to titrate the opioid to a dose that maintains a favorable balance

between analgesia and side effects). The addition of an adjuvant analgesic is one approach among many that may be considered for such patients [3]. (See "Cancer pain management with opioids: Optimizing analgesia", section on 'Dose titration' and "Cancer pain management with opioids: Prevention and management of side effects".)

As a general rule, a trial of a coanalgesic in the setting of poor opioid responsiveness should usually be considered only after efforts have been made to optimize opioid therapy (ie, by adjusting the dose or, if indicated, rotating to a different opioid). Adding a second analgesic only after the opioid has been optimized ensures that the second drug is needed, reduces the risk of additive toxicity by eliminating the need to titrate both drugs simultaneously, and limits confusion in determining the source of an adverse drug effect should one arise. (See "Cancer pain management with opioids: Optimizing analgesia", section on 'Opioid poorly responsive pain'.)

Available agents — The large and growing number of adjuvant analgesics can be categorized on the basis of how they are used in clinical practice [2]. This information is evolving as new trials are conducted, clinical experience expands, and as treatments that were developed for populations with noncancer pain are extrapolated to the cancer population. Based upon conventional practice, the categories of available agents include (table 1 and table 2):

- Drugs potentially useful for any type of pain (multipurpose analgesics)
- Drugs used for treatment of neuropathic pain
- Drugs used for bone pain
- Drugs used for pain and other symptoms in the setting of bowel obstruction

MULTIPURPOSE ANALGESICS — Some drug classes have been studied in diverse types of chronic pain. The evidence of broad analgesic efficacy supports the view that the specific agents within these classes (including glucocorticoids, antidepressants, alpha-2 adrenergic agonists, cannabinoids, and topical therapies) function as multipurpose analgesics that have potential value for any type of chronic pain.

Glucocorticoids — In palliative care, glucocorticoids are often used to alleviate symptoms such as pain, nausea, fatigue, anorexia, and malaise, and improve overall quality of life. A large body of clinical experience suggests that glucocorticoids may be beneficial for a variety of types of pain, including neuropathic and bone pain, pain associated with capsular expansion or duct obstruction, pain from bowel obstruction, pain caused by lymphedema, and headache caused by increased intracranial pressure. However, the randomized trials that have been conducted to assess the analgesic properties of glucocorticoids have been small, and produced mixed results [4-10]; a year 2013 systematic review of four of these randomized trials [4,7-9] concluded that the quality of the evidence was low and that no conclusion could be reached about the analgesic benefits of glucocorticoids [11]. More recently, an analgesic benefit for the use of glucocorticoids in patients with advanced cancer using opioids could not be shown in a trial in which 50 patients with cancer receiving opioids whose pain intensity was ≥4 on a scale of 1 to 10 were randomly assigned to methylprednisolone 16 mg twice daily or placebo for seven days [10]. At the seven-day evaluation point, there were no differences in mean pain intensity or relative analgesic consumption, but patients using methylprednisolone had significant short-term improvements in fatigue, appetite loss, and patient satisfaction. However, it is difficult to conclude from this very small study that analgesic benefits are not produced by glucocorticoid therapy, particularly in specific subgroups of cancer patients. (See "Assessment of cancer pain", section on 'Nociceptive pain' and "Management of vasogenic edema in patients with primary and metastatic brain tumors" and "Treatment and prognosis of neoplastic epidural spinal cord compression, including cauda equina syndrome".)

Choice of agent and dose — Dexamethasone is usually preferred for the management of cancer-related pain, presumably because of its long half-life and relatively low mineralocorticoid effects (table 3). However, there is no empiric evidence that this drug is either safer or more effective in the cancer population than any other glucocorticoid. Prednisone and methylprednisolone are acceptable alternatives. (See "Pharmacologic use of glucocorticoids".)

A typical regimen for patients with cancer-related pain is 1 to 2 mg of dexamethasone orally or parenterally twice daily; this may be preceded by a larger loading dose of 10 to 20 mg. This regimen, or comparable regimens of alternative steroids, is based upon clinical experience and is not evidence-based. Patients may do well with lower or higher doses, or with once-daily rather than twice-daily dosing.

Regardless of the regimen that is selected, the intent is usually for ongoing chronic use in the setting of advanced illness. In this situation, the risk of long-term toxicity, which includes myopathy, immunocompromise, psychotomimetic effects, and

hypoadrenalism, is attenuated by limited life expectancy and the need to address the multiple sources of suffering. (See "Major side effects of systemic glucocorticoids".)

There are some situations for which a brief regimen of high-dose glucocorticoids might be selected. Originally developed for the treatment of emerging epidural spinal cord compression (including cauda equina syndrome), a brief period of high-dose glucocorticoids is appropriate for any "pain crisis", which is defined as severe and escalating pain that is not responding sufficiently to an opioid.

In such cases, a typical regimen consists of a dexamethasone loading dose of 50 to 100 mg intravenously, which may be followed by 12 to 24 mg four times daily; this dose is then tapered over one to three weeks, usually as some other intervention, such as radiotherapy or a pain intervention (eg, neural blockade), is used to treat the pain.

Although the high-dose regimen is administered with the expectation that it will provide more rapid and substantial pain relief than a lower dose regimen, the only evidence for this originates from populations with epidural spinal cord compression, and even these data are conflicting [12]. Both the limited evidence and the potential for dose-related toxicity (which is clearly higher with higher dose regimens) must be recognized in weighing the potential benefits of the high-dose approach. This subject is addressed in detail elsewhere. (See "Treatment and prognosis of neoplastic epidural spinal cord compression, including cauda equina syndrome", section on 'Clinical trials'.)

Analgesic antidepressants — Antidepressants have been widely studied in populations with chronic pain, and the available data suggest that these drugs act as multipurpose analgesics [2,13-16]. Although very few of these studies have included cancer patients, the utility of these drugs for treatment of cancer pain has been extrapolated from data in other conditions.

In opioid-treated populations with advanced medical illness, antidepressants have been predominantly used for neuropathic pain. However, given the range of their potential analgesic efficacy, they could be considered for other types of chronic pain as well. (See 'Drugs used for neuropathic pain' below and "Assessment of cancer pain", section on 'Neuropathic pain'.)

Mechanism of analgesic effect — Antidepressants function as primary analgesics. Although pain reduction may be enhanced if there is a positive mood effect, analgesia is not dependent on mood elevation and pain can be improved in euthymic patients. If a patient with chronic cancer pain has depressed mood, a relatively early trial of an analgesic antidepressant is appropriate in the hope of achieving a separate and positive effect on mood.

The primary analgesic mode of action is thought to be related to enhanced availability of monoamines at synapses within neural pathways that are part of the descending pain modulating system. Inhibition of norepinephrine reuptake appears to be the most important mode of action, but serotonergic and dopaminergic effects also may play a role in analgesia. (See "Definition and pathogenesis of chronic pain".)

Selection of agent and dose — The antidepressants comprise several subclasses and numerous drugs (table 1). Analgesic efficacy is best established for some of the tricyclic compounds [13,17-19] and the serotonin-norepinephrine reuptake inhibitors (SNRIs) [16,19-22]; there is minimal evidence of analgesic efficacy with the serotonin-selective reuptake inhibitors (SSRIs) [13,23,24]. Benefit has also been suggested for bupropion (a dopamine reuptake inhibitor) in patients with neuropathic pain [25,26].

The tricyclic antidepressants include tertiary amines, such as amitriptyline, and secondary amines, such as nortriptyline and desipramine. The secondary amines are more selective at noradrenergic reuptake sites, and they have a more favorable side effect profile than does amitriptyline. As a result, when a tricyclic is chosen in a medically ill patient, desipramine or nortriptyline is usually preferred. All of the tricyclic compounds are relatively contraindicated in patients with serious heart disease, severe prostatic hypertrophy, and narrow-angle glaucoma. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Side effects'.)

There is strong evidence that at least some of the SNRIs (which include duloxetine, milnacipran, venlafaxine, and desvenlafaxine) have analgesic effects. Evidence of analgesic efficacy is best described with duloxetine [21,22], but the literature lacks trials in patients with cancer pain, and there are no comparative trials within the SNRI class.

Overall, the side effect profile of the SNRIs (which includes nausea, sexual dysfunction, and somnolence or mental clouding) is favorable relative to desipramine and nortriptyline. There is a great deal of individual variation, however. Among patients with serious medical illness, such as those with cancer, the first-line analgesic antidepressants to consider should be either a

secondary amine tricyclic compound (usually desipramine) or a SNRI (usually duloxetine), and the decision between these drugs usually is based on a case-by-case assessment of risk and cost.

Other antidepressants are considered as second-line drugs, typically considered if the initial therapeutic attempt yields side effects or a limited analgesic response. The exception is bupropion, a dopamine and norepinephrine reuptake inhibitor that is distinguished by its tendency to be activating. Given this latter effect, a trial of bupropion sometimes is considered early if cancer pain is complicated by fatigue or somnolence, even though the evidence of analgesic efficacy is weak. Bupropion should be avoided in patients at risk for seizures.

All of the analgesic antidepressants should be started at a relatively low initial dose (table 2). The starting dose for a trial of desipramine, for example, is 10 to 25 mg at night. The dose should be increased no more quickly than every few days in the absence of satisfactory relief or side effects. If analgesia is going to occur at any given dose, it typically appears within a week (developing more rapidly than the antidepressant effects). (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Early improvement and response'.)

Most patients who experience pain relief with desipramine respond at a dose between 50 and 150 mg per day. However, the tricyclics may have a drug concentration-response relationship for analgesia [17], and if neither analgesia nor intolerable side effects occur, continued dose escalation is reasonable. At relatively high doses (ie, above 100 mg per day), the plasma drug concentration and an electrocardiogram (ECG) should be checked. Tricyclic antidepressants can prolong the QTc interval and predispose to cardiac arrhythmias. These drugs should be used cautiously when a patient has known heart disease or is receiving other drugs (including methadone) that can prolong the QT interval (table 4). (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Plasma levels and therapeutic response' and "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Cardiac evaluation'.)

Other antidepressants such as duloxetine or bupropion should similarly be started at a relatively low initial dose (table 2), and titrated to conventional maximal doses to determine whether an analgesic or positive mood effect occurs. Unlike the tricyclics, these drugs do not prolong the QTc interval. However, gastrointestinal side effects (including nausea, dry mouth, and constipation) are common with duloxetine, and bupropion causes jitteriness or headache as relatively common initial side effects.

If possible, it is preferable to taper these drugs prior to discontinuation.

Other multipurpose analgesics — There are far fewer data supporting the use of the alpha-2 adrenergic agonists, cannabinoids, and topical therapies as multipurpose analgesics for the treatment of cancer pain.

Alpha-2 adrenergic agonists — Classification of alpha-2 adrenergic agonists such as clonidine and tizanidine as multipurpose analgesics is supported by both animal and human studies. Clonidine, which can be administered orally, transdermally, or intraspinally, has been mainly studied in patients with noncancer-related chronic pain. Spinally-administered clonidine has analgesic properties in patients with cancer pain and is more efficacious for neuropathic than nociceptive pain [27]. (See "Cancer pain management: Interventional therapies".)

There is less evidence of analgesic efficacy with tizanidine, an orally active centrally acting alpha-2 agonist that is approved as an antispasticity agent [28], or the parenteral alpha-2 agonist dexmedetomidine [29,30]. However, this class of drugs can provide analgesia in diverse types of pain. Although the mechanism is unknown, the analgesic effects presumably relate to increased activity in monoamine-dependent, endogenous pain modulating pathways in the spinal cord and brain.

The alpha-2 agonists produce somnolence and dry mouth, and may cause hypotension, which is usually orthostatic. This potential, combined with analgesic efficacy that appears to be lower than with other multipurpose drugs, indicates a limited role for these drugs in the medically ill.

Tizanidine has less hypotensive effect than clonidine and could be considered for a trial in patients with opioid-refractory neuropathic pain. Patients who are hemodynamically unstable, predisposed to serious hypotension (eg, by autonomic neuropathy, intravascular volume depletion, or concurrent therapy with potent hypotensive agents), or encephalopathic from other causes are not appropriate candidates. Dosing with tizanidine may be initiated just at bedtime in an effort to provide hypnotic effects. If the drug is tolerated, dose escalation using two divided daily doses is typically used when the intent of therapy is analgesia.

Cannabis and cannabinoids — Cannabinoids are derived from the cannabis (marijuana) plant, which contains over 400 compounds, including more than 60 cannabinoids. The primary psychoactive cannabinoid is delta-9-tetrahydrocannabinol (THC, also known as dronabinol). In vivo, cannabinoid molecules such as THC interact with an endogenous system that includes cannabinoid-like ligands (the endocannabinoids) as well as multiple receptors in both the periphery and central nervous system. (See "Cannabis use disorder: Epidemiology, comorbidity, and pathogenesis".)

Although concern about the abuse potential of cannabinoid drugs has slowed their development, several cannabinoid-type drugs are commercially available, and others are under study. The available data suggest that these compounds may be useful as multipurpose analgesics in palliative care populations [31-35], although few studies have been conducted in cancer patients [36].

An oromucosal spray containing THC plus cannabidiol (and smaller concentrations of other compounds), nabiximols (Sativex), is approved in Canada and elsewhere (but not yet in the United States) for treatment of neuropathic pain due to multiple sclerosis and as an adjunctive treatment for pain in patients with advanced cancer [37]. It is rapidly absorbed from the buccal mucosa, and the dose can be self-titrated by the patient.

The benefit of nabiximols for management of cancer pain was shown in a double-blind trial in which 177 cancer patients with inadequate analgesia despite chronic opioid dosing were randomly assigned to nabiximols (n = 60), THC alone (n = 58), or placebo (n = 59) for two weeks; doses were self titrated (with maximum permitted doses) until satisfactory relief or untoward side effects [34]. By the end of the study period, compared to placebo, the adjusted mean reduction in pain score from baseline was significantly higher with nabiximols, but not with THC alone. In addition, there was a nonsignificant trend toward fewer daily doses of all breakthrough medications in the nabiximols group, compared to placebo. However, there were imbalances in the baseline opioid dose that could have biased the results in favor of nabiximols. There was no evidence of loss of effect for the relief of cancer pain with long-term use of nabiximols [38].

Until newer cannabinoid preparations such as nabiximols become available in the US, clinical use of cannabinoids for cancer pain is limited to those agents that are marketed for purposes other than pain, including THC and nabilone. A trial of one of these drugs is usually considered only in those patients who are refractory to opioids and other appropriate adjuvant analgesics; most will have neuropathic pain. Nabilone should be started at 0.5 to 1 mg at night and titrated up to 3 mg twice daily, or higher if tolerated. Dronabinol usually is started at a dose of 2.5 mg once or twice daily, and titrated.

The most common side effects associated with the cannabinoids are dizziness, somnolence, and dry mouth.

The use of medical marijuana for refractory cancer pain is very controversial. Medical use of marijuana is legal in several countries, including the Netherlands and Canada. However, despite legalization by several states, marijuana use is still illegal in the United States at the federal level (which considers marijuana a schedule I controlled substance), and individuals prescribing or using marijuana for medical use are at risk for prosecution [39].

Although severe or chronic pain accounts for over 90 percent of the qualifying conditions for use of medicinal marijuana among registered users in several states in which it is legal [40-43], there are no controlled studies demonstrating the efficacy of inhaled marijuana as an adjunct to traditional pain medications for patients with cancer-related pain. Particularly in view of concerns for increased rates of respiratory infections and pneumonia among cannabis smokers and uncertainty about higher cancer rates in this population as well [36,44,45], its use cannot be recommended.

Topical therapies — Topical therapies have the potential to deliver analgesic compounds directly to the site that is presumably responsible, at least in part, for the persistent pain. The relative lack of systemic toxicity offers a therapeutic advantage that may be particularly relevant to the medically ill. Although topical analgesics have been used mostly for neuropathic pain, they have the potential for broader application. An overview of topical analgesics for treatment of superficial painful conditions is provided in the table (table 5).

Lidocaine — The most widely used topical therapies for pain contain local anesthetics. Lidocaine 5 percent transdermal patches are widely used for the treatment of focal and/or regional pain of all types. The evidence to support benefit is relatively weak, and consists of small, short-term, open-label nonrandomized studies that were conducted in patients with postherpetic neuralgia [46], and other noncancer disorders causing chronic pain [47,48]. Although the current approved use (based on clinical trials) is a 12 hour per day dosing regimen, some patients find that pain relief does not last 24 hours and continuous

application is common in the clinical setting. Multiple patches are often used together. There are limited data that indicate a high level of safety with four patches applied for 24 hours a day for up to 72 hours [49].

The most frequently reported adverse event is mild to moderate skin irritation at the patch application site, which seems to be related to the vehicle rather than to lidocaine. There is only a remote risk of toxicity from systemic absorption of lidocaine. Cost may be prohibitive.

Other local anesthetics — Topical analgesia also may be possible using creams or gels containing local anesthetics:

- A commercially available mixture of prilocaine and lidocaine, known as eutectic mixture of local anesthetics (EMLA) cream, is capable of penetrating the skin and producing a dense local cutaneous anesthesia [50]. This product and others have been approved to prevent the pain of needle puncture or incision. In cancer patients with a peripheral source of pain, application of a thin layer under an occlusive dressing has been used as an adjunct to chronic therapy. The treatment is relatively expensive and difficult to sustain for long periods.
- Surveys of studies using relatively high concentrations of topical lidocaine gel suggest that a compound of this type can produce similar benefits for focal, peripherally-generated pain [51]. Although there is a remote risk of toxicity from systemic absorption, the safety of the lidocaine patch or compounded creams suggest that a trial should be considered in patients who have pain that is localized to a relatively small area.
- Capsaicin, the naturally occurring constituent of the chili pepper, depletes substance P from the terminals of afferent C-fibers. Topical application of a commercially available capsaicin cream or low-dose transdermal patch (which are available over the counter in the US) or a single application of a high-dose patch (8 percent capsaicin, Qutenza, which requires a prescription, (table 5)) has yielded weak to moderate analgesic effects in controlled trials focusing on patients with various types of neuropathic and joint pain [52-54]. Burning at the application site, which is often transitory, is the major side effect and may be limiting. Application three to four times daily for a period of at least a week is needed to determine benefit.

Antiinflammatory and antidepressant drugs — Numerous anti-inflammatory drugs have been investigated for topical use; diclofenac patch, cream, and gel are commercially available in the US; others are available outside of the US (table 5).

Like capsaicin, there is some evidence that diverse types of pain may respond favorably. Although data from controlled trials in populations with musculoskeletal pain are conflicting [55,56], there is sufficient evidence of effectiveness and safety to warrant a therapeutic trial in patients with small areas of pain related to neuropathic or nociceptive mechanisms. (See "Assessment of cancer pain", section on 'Inferred pathophysiology (types of cancer pain)'.)

Evidence for the analgesic efficacy of topical tricyclic antidepressants is conflicting [57], but a cream containing doxepin is commercially available and approved for the short-term management of pruritus. Given the safety of this approach, a trial of topical doxepin may be considered for the patient with local or regional pain. (See "Pruritus: Overview of management".)

Other drugs have been used empirically in specially compounded creams for use in patients with pain. The most popular are ketamine and gabapentin, but a variety of others are in use. Supporting data are very meager or absent, but given the relative safety of topical application of these agents, a clinical trial may be reasonable. Cost must be considered when recommending these strategies.

DRUGS USED FOR NEUROPATHIC PAIN — All of the drugs classified as multipurpose analgesics may be considered for a clinical trial in patients with opioid-refractory neuropathic cancer pain. However, the most important of the multipurpose adjuvant analgesics for treatment of neuropathic pain are the analgesic antidepressants and anticonvulsants.

Anticonvulsant analgesics — The anticonvulsants represent a diverse group of drugs that vary in mechanisms and clinical effects (table 1 and table 2). Analgesic effects are best characterized for gabapentin and pregabalin, two drugs that are now considered the first-line approach for patients without comorbid depression who have non-chemotherapy-related neuropathic cancer pain that is refractory to opioid analgesics [58].

Gabapentin and pregabalin — Gabapentin and pregabalin have been extensively studied in diverse types of neuropathic pain, particularly postherpetic neuralgia and painful diabetic neuropathy [59-66]. Fewer data are available in patients with neuropathic pain related to cancer or its treatment [60,67-72]:

- In two randomized placebo-controlled trials involving populations of opioid-treated patients with cancer-related neuropathic pain, gabapentin and pregabalin were each significantly better than placebo in improving neuropathic pain and dysesthesias [60,67]; one of these trials directly compared gabapentin and pregabalin, and is discussed in more detail below [67].
- On the other hand, another randomized trial of gabapentin versus placebo for chemotherapy-induced painful peripheral neuropathy failed to show any benefit for gabapentin. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Anticonvulsants'.)
- A systematic review of the effectiveness of antiepileptic drugs or antidepressants added to opioids for neuropathic pain from cancer concluded that benefit from any adjuvant was modest and much less than that seen in patients with noncancer neuropathic pain, strongest for gabapentin, and counterbalanced by an increase in adverse events [73].
- In contrast, a second systematic literature review of the evidence for pharmacologic treatment of neuropathic cancer pain concluded that the absolute risk benefit for all agents (antidepressants, anticonvulsants) greatly outweighed the absolute risk for harm, but that all studies had low methodologic quality that precluded drawing conclusions about the relative effect sizes of the different medication groups [74].

Gabapentin and pregabalin both act by binding to the alpha-2 delta protein modulator of the N-type, voltage-gated calcium channel. Binding to this protein reduces calcium influx into the neuron, and lessens the likelihood of depolarization.

Unlike all other anticonvulsants, gabapentin and pregabalin are not metabolized in the liver and they have no known drug-drug interactions. Both drugs are excreted by the kidneys, which necessitates dose reduction in the setting of renal impairment. Their main side effects are mental clouding, dizziness, and somnolence; edema and weight gain are less common.

The main difference between gabapentin and pregabalin is pharmacokinetic. Absorption and entry of gabapentin into the central nervous system (CNS) is facilitated by a saturable transporter in the small bowel and CNS. At relatively higher doses (approximately 1800 mg per day, but could be higher or lower in individual cases, (table 2)), the kinetics become nonlinear and there is less complete absorption with each dose increment. These saturable kinetics mean that gabapentin has a pharmacokinetic "ceiling", which coexists with a possible pharmacodynamic "ceiling" of the type that is observed with all adjuvant analgesics (ie, at some point, a maximum effect is reached even if the plasma concentration of the drug is further increased).

In contrast, absorption of pregabalin is not dependent on a saturable transport mechanism, and this drug only has the unpredictable pharmacodynamic ceiling. This linear pharmacokinetic profile simplifies dosing of pregabalin compared to gabapentin.

Whether either drug is superior to the other for treatment of neuropathic pain is unclear. A double-blind trial randomly assigned 120 patients with cancer and severe neuropathic pain to gabapentin (900 mg daily for one week followed by 1200 mg daily for one week, then 1800 mg daily), pregabalin (150 mg daily for one week, followed by 300 mg daily for one week, then 600 mg daily), amitriptyline (50 mg daily for one week followed by 75 mg per day for one week, then 100 mg daily at bedtime), or placebo [67]. The primary outcome measure was global intensity of pain, as measured on a 100 mm Visual Analog Scale (VAS). By week four, the mean VAS score with pregabalin was significantly less than that of the patients receiving gabapentin, and the percentage of patients requiring rescue morphine in the placebo, amitriptyline, gabapentin, and pregabalin groups was significantly different (100, 57, 33, and 17 percent, respectively).

This study suggests that pregabalin may have superior efficacy but the limitations of the study (no indication of how randomization or blinding was performed, no power analysis, and the primary endpoint analysis was not an "intention to treat" analysis) preclude definitive conclusions. In addition, the drugs were tested at doses that may not be fairly compared; the initial dose of pregabalin was relatively high while the top dose of gabapentin was the minimum dose that is often chosen. For all of these reasons, it cannot be concluded that pregabalin is superior to gabapentin for treatment of neuropathic pain.

The starting dose of pregabalin is usually 50 to 75 mg per day in two divided doses (a lower dose should be used in the medically frail), and escalation to the usual effective dose of 150 to 300 mg twice daily typically is accomplished in two to three steps over one week. In the medically frail cancer patient, gabapentin is often initiated at a dose of approximately 100 to 300 mg per day (one-half the dose of a non-frail patient). The dose is gradually escalated every few days while monitoring

analgesia and side effects. If pain relief does not occur, in the absence of an analgesic ceiling or adverse effects, dose escalation can extend to 3600 mg per day administered in two to three divided doses and sometimes higher.

Controlled trials of pregabalin that have included "gabapentin failures" have shown that patients may respond to pregabalin even if gabapentin was not tolerated [69]. Given these data and extensive clinical observations, it is appropriate to consider a trial of the alternate drug if an attempt with the first does not yield benefit.

If possible, it is preferable to taper these drugs prior to discontinuation.

Other anticonvulsants — Numerous other anticonvulsants have been studied as analgesics [75]. Older anticonvulsant such as carbamazepine, valproate, and phenytoin are perceived as having potential analgesic effects based on trials performed several decades ago [76]. Carbamazepine remains a preferred drug for trigeminal neuralgia, but in the cancer population, it is seldom used because of the risk of leucopenia and the need for monitoring myelosuppressive effects. (See "Trigeminal neuralgia".)

The data supporting the analgesic efficacy of valproate and phenytoin are limited. Although these drugs may be considered for trials in patients with intractable neuropathic pain, conventional practice in countries that have access to newer agents relegates them to trials after other anticonvulsants have been demonstrated to be ineffective.

Lamotrigine has been effective in studies of central pain, trigeminal neuralgia, and painful HIV polyneuropathy [62], but it has not been analgesic in other trials, including one conducted in patients with chemotherapy induced painful peripheral neuropathy [77]. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Anticonvulsants'.)

Lamotrigine is associated with a small risk of severe cutaneous hypersensitivity, which is relatively higher in younger patients. The drug should not be used in patients under the age of 15, and slow titration of the dose from a low initial dose is necessary to reduce the risk of hypersensitivity.

The need for this slow initial titration, which ideally requires more than one month to reach a dose that might be effective, as well as the risk of Stevens-Johnson syndrome, diminishes enthusiasm for an early trial of lamotrigine. Typically, it is considered only after trials of several preferred drugs for neuropathic pain have been ineffective.

Oxcarbazepine is a metabolite of carbamazepine, which has similar anticonvulsant properties and a safer pharmacologic profile. Although studies have not been uniformly positive, it has been shown to be analgesic in trigeminal neuralgia and several other types of neuropathic pain [78]. Like lamotrigine, a trial may be considered after trials of the alpha-2-delta modulators and perhaps one or two of the analgesic antidepressants have proved to be ineffective.

Other anticonvulsants may be considered for treatment-refractory cancer-related neuropathic pain [2,75]:

- Topiramate, an effective drug for migraine, has been variably effective in studies of neuropathic pain, but anecdotal experience suggests that some patients respond and derive substantial benefit [79].
- There are conflicting reports on the analgesic efficacy of levetiracetam, zonisamide, and tiagabine, and in the absence of additional data, these drugs usually are not considered unless others are not available.
- Clonazepam is a benzodiazepine. Very meager data support analgesic efficacy in patients with neuropathic pain [80]; its anxiolytic effects may be favorable, however, and a trial often is considered in the patient with refractory neuropathic pain associated with anxiety.
- Lacosamide, a relatively new anticonvulsant, is a sodium channel modulator, a unique mechanism of action. Large controlled trials in patients with painful diabetic neuropathy suggest benefit [81], although there are no data in patients with cancer-related pain. This agent could be considered among those that are potentially useful for treatment of refractory neuropathic pain.

None of these agents has been studied in patients with chemotherapy-induced peripheral neuropathy. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Pharmacologic agents'.)

Antidepressants — As described previously, the most useful of the analgesic antidepressants are the serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine, and the secondary amine tricyclic compounds (eg,

desipramine). Evidence of analgesic efficacy for chronic pain has been demonstrated in randomized controlled trials and meta-analyses. (See 'Analgesic antidepressants' above.)

Although trials comparing antidepressants versus other strategies (such as anticonvulsants) for treatment of neuropathic pain are lacking, most experts consider these drugs to represent preferred first-line treatments for neuropathic pain that is associated with significant depressed mood, and appropriate second-line agents (after the alpha-2-delta modulators gabapentin or pregabalin, see below) for non-depressed patients who have neuropathic pain [58]. (See 'Analgesic antidepressants' above.)

The systematic review of the effectiveness of antiepileptic drugs or antidepressants added to opioids for neuropathic pain from cancer described above concluded that benefit from any adjuvant was modest and much less than that seen in patients with noncancer neuropathic pain, strongest for gabapentin, and counterbalanced by an increase in adverse events [73].

A second systematic literature review of the evidence for pharmacologic treatment of neuropathic cancer pain concluded that the absolute risk benefit for all adjuvant analgesics, including antidepressants, greatly outweighed the absolute risk for harm, but that all studies had low methodologic quality that precluded drawing conclusions about the relative effect sizes of antidepressants relative to any other medication groups [74].

However, positive results with duloxetine in a single randomized, double-blind placebo-controlled crossover trial conducted in patients with painful chemotherapy induced peripheral neuropathy after treatment with taxanes or platinum-containing chemotherapy supports the view that in this setting, duloxetine is an appropriate first-line agent, particularly in view of a negative gabapentin trial. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Duloxetine and other antidepressants' and "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Anticonvulsants'.)

However, additional data will be needed to establish the superiority of duloxetine or any other antidepressant over an alpha-2-delta modulator in these patients. (See 'Gabapentin and pregabalin' above.)

Other drugs used for neuropathic pain — Other drug classes play a far less prominent role in the clinical strategy for cancer-related neuropathic pain. Nonetheless, occasional patients with refractory neuropathic pain may be candidates for a trial of one or more of these uncommon treatments.

Other multipurpose analgesics — Among the drug classes used less often are those previously grouped with the multipurpose analgesics. A trial of an alpha-2 agonist such as tizanidine, or a trial of a cannabinoid such as dronabinol, might be considered in refractory cases of neuropathic pain. (See 'Alpha-2 adrenergic agonists' above and 'Cannabis and cannabinoids' above.)

Topical analgesics — Topical agents, usually a local anesthetic, may also be considered for an early trial when neuropathic pain is focal or regional and opioid therapy is not sufficient. At least one trial suggests potential benefit for a topical gel containing baclofen, amitriptyline, and ketamine in patients with painful chemotherapy induced peripheral neuropathy. (See 'Topical therapies' above and "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Topical treatments containing amitriptyline and ketamine with and without baclofen'.)

Sodium channel blockers — Blockade of sodium channels has been recognized as an analgesic mechanism for decades and the potential role of the new sodium channel modulator, lacosamide, was mentioned above (see 'Other anticonvulsants' above).

Treatment approaches using older sodium channel blockers include oral therapy with antiarrhythmic drugs, such as mexiletine or tocainide, or parenteral therapy, usually with lidocaine. A brief intravenous infusion of lidocaine, typically 2 to 4 mg/kg infused over 20 to 30 minutes in a monitored setting, can be extremely useful in the management of severe neuropathic pain, resulting in prompt pain reduction so that other strategies can be implemented more gradually. The analgesic effects and generally favorable safety profile of these drugs are strongly supported by the literature [82,83]; the usual side effects are dizziness, nausea, and fatigue.

Ketamine and other NMDA receptor antagonists — The N-methyl-D-aspartate (NMDA) receptor is involved in both the sensitization of central neurons and the functioning of the opioid receptor, and there is good evidence that one of the commercially available NMDA receptor antagonists, ketamine, has analgesic properties [84]. At subanesthetic doses, ketamine

may be used as a brief infusion for treatment of severe refractory pain [85,86], as a more prolonged infusion (typically at the end of life), or as oral therapy [87]. The evidence to support benefit of ketamine as an adjuvant to opioid therapy is quite limited. In all, five randomized trials have been conducted:

Three small trials conducted in 1996, 1999 and 2000 suggested enhanced control of cancer pain when ketamine was given with morphine [88-90] Three later randomized trials, one conducted in 20 patients with refractory cancer pain, one in 30 patients receiving morphine for treatment of cancer pain, and another in 185 patients with refractory chronic pain related to cancer or its treatment, failed to demonstrate any benefit from the addition of infusional or oral ketamine to opioids [91-93]. In the largest of the three trials, only 39 of the original 93 patients allocated to ketamine received the full five days of planned treatment, with approximately equal numbers discontinuing therapy for lack of efficacy and treatment-related toxicity (somnolence, constipation, nausea/vomiting, dizziness, cognitive disturbance) [92]. Only 35 of the original 91 patients assigned to placebo received the full five days of planned treatment, but nearly all of the dropouts were for treatment failure. A 2012 Cochrane review [94] of two of these randomized trials [88,90] (the rest were excluded because of methodologic problems or extremely small number of patients completing the study) concluded that the evidence was insufficient to assess the effectiveness of ketamine in this setting.

Nevertheless, this approach continues to be used by experienced pain clinicians, particularly in the setting of otherwise refractory neuropathic pain at the end of life, based mainly upon favorable anecdotal experience [85,86]. The side effect profile of ketamine, including particularly psychotomimetic effects and delirium, is problematic, however; and as a result, the most common use is short-term therapy in a monitored setting. Based upon anecdotal observations that treatment with a benzodiazepine, such as lorazepam, or a neuroleptic, such as haloperidol, reduces the risk of psychotomimetic effects from ketamine, most practitioners co-administer one of these drugs prior to the start of the infusion and repeatedly during longer term treatment; a benzodiazepine usually is preferred [95]. Gradual dose titration of the ketamine may also reduce the incidence of psychotomimetic effects [96].

Other NMDA receptor antagonists, such as memantine, amantadine and dextromethorphan, have been studied in neuropathic pain states, with mixed results [97]. They are rarely considered for trials in cancer-related neuropathic pain that has not responded to other agents.

GABA receptor inhibitors and agonists — Among the gamma aminobutyric acid (GABA) receptor inhibitors are the benzodiazepines, which affect the GABAA receptor subtype, and baclofen, which affects the GABAB subtype. As noted previously, the only benzodiazepine that is typically used for neuropathic pain is clonazepam. (See 'Other anticonvulsants' above.)

Baclofen, a selective GABAB agonist, is an antispasticity drug with established efficacy in trigeminal neuralgia. It has been used anecdotally for neuropathic pain of other types, including cancer pain [98]. A low starting dose of 5 mg twice daily can be gradually escalated to doses that may exceed 200 mg per day in some patients.

SUMMARY AND RECOMMENDATIONS OF EXPERT GROUPS — Opioids are widely used for treatment of cancer pain because of their safety, ease of titration, reliability, and effectiveness for all types of pain, including neuropathic pain. Although neuropathic pain may be more difficult to treat, a favorable response to opioid-based analgesia is often possible. (See "Assessment of cancer pain" and "Cancer pain management with opioids: Optimizing analgesia".)

For this reason, some experts advocate a trial of an adjuvant analgesic for cancer-related neuropathic cancer pain only in the setting of relatively poor opioid responsiveness, ie, after an opioid has been titrated to optimize the balance between analgesia and side effects. This view is somewhat controversial, however, and others advocate early use of adjuvant analgesics, usually in tandem with cautious opioid titration.

Experts generally agree that this first-line or concurrent use of an opioid should be considered only in patients with active cancer; patients with no active disease (such as those with posttreatment neuropathic pain like a postmastectomy pain syndrome) are usually similar to patients with neuropathic pain that is not cancer-related. In these situations, opioid therapy is usually perceived to have a more limited role. The choice of therapy may also be influenced by the type of neuropathic pain. For example, guidelines from the American Society of Clinical Oncology recommend duloxetine for initial treatment of chemotherapy-induced painful peripheral neuropathy. (See "Prevention and treatment of chemotherapy-induced peripheral

neuropathy", section on 'Recommendations of expert groups' and "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Duloxetine and other antidepressants'.)

Given the weight of evidence, we consider analgesic antidepressants such as SNRIs or tricyclics to represent first-line treatments for neuropathic pain that is associated with significant depressed mood, and second-line (after the alpha-2-delta modulators gabapentin or pregabalin) in non-depressed patients who have neuropathic cancer pain that is refractory to opioid therapy. Given the positive duloxetine trial, and negative trials of gabapentin and other anticonvulsants as well as tricyclic antidepressants in patients with painful chemotherapy-induced peripheral neuropathy, we prefer duloxetine in this setting. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Pharmacologic agents'.)

Guidelines for treatment of neuropathic pain from the International Association for the Study of Pain (IASP) focus on noncancer pain populations, and recommend first-line use of selected anticonvulsants (specifically gabapentin or pregabalin) or an analgesic antidepressant (either a secondary amine tricyclic antidepressant such as nortriptyline or desipramine or an SNRI such as duloxetine or venlafaxine) [58]. An analgesic antidepressant should be tried initially if the patient has a depressed mood. The guidelines indicate that opioid analgesics either alone or in combination with an analgesic adjuvant should be considered for patients with neuropathic cancer pain, as well as for episodic exacerbations of severe pain, or when prompt pain relief during titration of an adjuvant analgesic is needed.

Guidelines from the National Comprehensive Cancer Network (NCCN) and the European Association for Palliative Care [99] broadly concur with the IASP guidelines, suggesting that antidepressants or anticonvulsants are preferred first-line coanalgesics for the treatment of cancer-related neuropathic pain in patients whose pain is only partially responsive to opioids.

A stepwise approach to assessment and treatment is recommended in the IASP guidelines and is relevant to neuropathic cancer pain [58]:

- Assessment of the pain and establishment of the likely neuropathic etiology. The assessment should also include identification of relevant comorbidities which may be impacted by treatment of neuropathic pain, or require modifications in the initial treatment regimen. (See "Assessment of cancer pain".)
- Initiate antineoplastic therapy for the disease causing the neuropathy, if applicable.
- Initiate symptom treatment for the painful neuropathy.

ADJUVANT DRUGS USED FOR BONE PAIN — The assessment of a patient with new bone pain may suggest the need for radiation therapy or an intervention such as kyphoplasty or surgery. (See "Assessment of cancer pain" and "Radiation therapy for the management of painful bone metastases" and "Evaluation and management of complete and impending pathologic fractures in patients with metastatic bone disease, multiple myeloma, and lymphoma".)

Patients with multifocal pain usually are managed with a non-steroidal antiinflammatory agent (NSAID), unless they have a specific contraindication to use of these agents, and an opioid, with or without an adjuvant analgesic used specifically for bone pain. (See "Cancer pain management: Use of acetaminophen and nonsteroidal antiinflammatory drugs", section on 'Indications and contraindications'.)

In addition to a glucocorticoid, such as dexamethasone, drugs to consider in this setting include bisphosphonates, calcitonin, and bone-seeking radionuclides (table 1).

Osteoclast inhibitors

Bisphosphonates — For patients with metastatic bone disease, bisphosphonates prevent skeletal-related events, including fracture, and they may also improve pain and quality of life. Bisphosphonates act by directly inhibiting osteoclast activity, stimulating osteoblasts to produce osteoclast-inhibiting factor, and causing osteoclast apoptosis.

There are substantial data supporting the analgesic potential of all of the parenteral bisphosphonates, including pamidronate, zoledronic acid, ibandronate, and clodronate (not available in the US), as well as oral ibandronate and clodronate. In a Cochrane review, a significant improvement in bone pain was reported after receiving a bisphosphonate in patients with bone metastases from breast cancer in 6 of 11 studies [100]. (See "Osteoclast inhibitors in the management of bone metastases from breast cancer", section on 'Bisphosphonates'.)

Comparative data are very limited, and the specific drug is chosen on the basis of experience, cost and convenience. This subject is addressed in more detail elsewhere. (See "Bisphosphonates and denosumab in patients with metastatic cancer".)

Although generally well tolerated, the bisphosphonates are associated with some side effects (see "Risks of therapy with bone modifying agents in patients with advanced malignancy"):

- These drugs can impair renal function, but this is usually a transitory problem. Renal function should be checked prior to treatment, and if impaired, the starting dose should be lowered and the patient carefully monitored. Severe renal insufficiency is a relative contraindication to therapy.
- A temporary flu-like syndrome with fever and body aches commonly follows treatment initiation. Treatment with acetaminophen may be helpful.
- Hypocalcemia is possible when these drugs are administered even to normocalcemic patients. These patients usually are subsequently found to be vitamin D deficient. The calcium level should therefore be monitored during therapy.
- An unusual complication, osteonecrosis of the jaw, is characterized by painful erosions, ulcers, and sinus tracts in the mandible, and occasionally, the maxilla. This complication usually occurs after months of treatment and may be relatively more common during therapy with pamidronate and zoledronic acid than with other bisphosphonates; it is rare during oral therapy. Given the evidence that oral trauma and dental infections increase the risk of this complication, patients with bone pain and very poor dentition, jaw infection, or recent substantial dental procedures should be considered for an alternative pharmacologic strategy. (See "Risks of therapy with bone modifying agents in patients with advanced malignancy", section on 'Osteonecrosis of the jaw'.)

Denosumab — Osteoclast inhibition can also be achieved by targeting receptor activator of nuclear factor kappa B ligand (RANKL), a key component in the pathway for osteoclast formation and activation. Denosumab, a monoclonal antibody targeting RANKL, has been compared to zoledronic acid in patients with metastatic bone disease from a variety of solid tumors; all have concluded that there is a slight benefit to denosumab in terms of preventing skeletal-related events, but only one of the trials has reported endpoints related to bone pain [101]. In this trial comparing zoledronic acid versus denosumab in 2046 patients with advanced breast cancer and bone metastases, 43 percent of patients reported moderate to severe pain at baseline, although only approximately 16 percent were using strong opioids. Compared with the zoledronic acid group, fewer patients receiving denosumab who had no or mild pain at baseline progressed to moderate or severe pain (although the absolute difference was only 5 percent), there was an almost four month longer delay in the median time to pain worsening to moderate or severe, and fewer shifted from no or low analgesic use to strong analgesic use. However, palliation of pain severity as measured by the proportion of patients with meaningful improvement in pain (defined as a decrease of ≥2 points in the worst pain score), median time to meaningful improvement in worst pain score, and the time to decreased pain interference, was similar for both treatment groups. Thus, the analgesic superiority of denosumab relative to that of bisphosphonates for patients with painful bone metastases is not yet established. (See "Bisphosphonates and denosumab in patients with metastatic cancer" and "Bone metastases in advanced prostate cancer: Management" and "Overview of the use of osteoclast inhibitors in early breast cancer".)

Calcitonin — Small controlled trials have yielded conflicting information about the potential for subcutaneous calcitonin to reduce metastatic bone pain [102]. Given the lack of consistent evidence, this treatment generally is not recommended, although an empirical trial could be considered when other treatments are unavailable or ineffective.

Bone-targeted radioisotopes — Bone-seeking radioisotopes, such as strontium-89 and samarium-153, link a short-lived radiation source to a bisphosphonate molecule. Once injected, the drug is taken up at the site of bone metastases, and delivers radiation focally.

Although bone-targeted radioisotopes can be a useful treatment for multifocal bone pain, myelosuppression is a significant concern (although less with samarium than with strontium), and treatment requires special skills and facilities. If available, this approach is typically considered for the patient with refractory multifocal bone pain, whose blood counts are not very low, and who is not expected to require myelosuppressive chemotherapy in the near future.

These agents have been used most often for men with metastatic prostate cancer; their use is discussed in more detail elsewhere. (See "Bone metastases in advanced prostate cancer: Management", section on 'Bone-targeted radiopharmaceuticals'.)

DRUGS USED FOR THE PAIN OF BOWEL OBSTRUCTION — Bowel obstruction is a well-recognized complication in patients with advanced intraabdominal or pelvic tumors. Most of these patients are inoperable, and their survival is generally short. Some cases may be amenable to placement of a self-expanding metal stent [103]. (See "Enteral stents for the management of malignant colorectal obstruction".)

For patients with inoperable intestinal obstruction who are not appropriate for a stent, management with IV fluids and placement of a nasogastric tube for decompression has been the conventional approach historically. Decompression of gastric contents can also be achieved by placement of a percutaneous gastrostomy tube. However, these procedures provide only incomplete relief of distressing symptoms, and the ongoing presence of these tubes can be uncomfortable and distressing for the patient and his or her family.

More recently, medical management of inoperable patients has focused on adequate control of pain, distention, and vomiting using hydration, opioids, and adjuvant analgesics that may reduce symptoms by lessening peritumoral edema (glucocorticoids) and diminishing intraluminal secretions and peristaltic movements (anticholinergic agents and octreotide). Anticholinergic drugs (scopolamine, glycopyrrolate) and octreotide both reduce propulsive as well as nonpropulsive gut motility, and they decrease intraluminal secretions.

This subject is discussed in detail elsewhere. (See "Palliative care: Assessment and management of nausea and vomiting", section on 'Gastrointestinal obstruction'.)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword (s) of interest.)

- Basics topics (see "Patient information: Managing pain when you have cancer (The Basics)")

SUMMARY AND RECOMMENDATIONS — Adjuvant analgesics (coanalgesics) are drugs that were originally marketed for indications other than pain but are potentially useful as analgesics. Many of these drugs are useful for treatment of chronic cancer pain, and in those with active disease, usually are considered when a patient is poorly responsive to opioids. (See 'Definition of an analgesic adjuvant' above.)

The available agents are categorized on the basis of how they are used in clinical practice (table 1). (See 'Available agents' above.)

For all types of pain

- Glucocorticoids may be beneficial for a variety of types of pain, including neuropathic and bone pain, pain associated with capsular expansion or duct obstruction, pain from bowel obstruction, pain caused by lymphedema, and headache caused by increased intracranial pressure. However, specific recommendations for use of glucocorticoids in the treatment of cancer-related pain are not evidence-based due to limitations in the existing literature. Recommendations are based upon anecdotal experience. (See 'Glucocorticoids' above.)

  In the setting of chronic pain, a typical regimen is dexamethasone 1 to 2 mg twice daily; this may be preceded by a larger loading dose of 10 to 20 mg. A brief period of high-dose glucocorticoids (eg, dexamethasone 50 to 100 mg IV, followed by 12 to 24 mg four times daily, tapered over one to three weeks) is appropriate for "pain crisis" (severe and escalating pain that is not responding sufficiently to an opioid). (See 'Choice of agent and dose' above.)

- For a patient with chronic cancer pain that is poorly responsive to opioid therapy who also has a depressed mood, we suggest an early trial of an analgesic antidepressant (**Grade 2B**). Options include a serotonin-norepinephrine reuptake inhibitor (SNRI) such as duloxetine or a secondary tricyclic drug such as desipramine; bupropion may be considered if cancer pain is complicated by fatigue or somnolence. (See 'Analgesic antidepressants' above.)

- A trial of a transdermal lidocaine patch could be considered in patients who have focal, peripherally-generated pain. Other topical treatments that may be useful in these patients are creams containing a local anesthetic, a NSAID, or capsaicin. (See 'Topical therapies' above.)

- Where available, use of an oromucosal spray containing THC plus cannabidiol (and smaller concentrations of other compounds, nabiximols [Sativex]) may be useful as an adjunctive treatment for refractory pain in patients with advanced cancer. (See 'Cannabis and cannabinoids' above.)

Neuropathic pain — Any of the drugs classified as multipurpose adjuvant analgesics could be considered for a clinical trial in patients with opioid-refractory neuropathic cancer pain. The following reflects our general approach to these patients:

- If neuropathic pain refractory to an opioid is associated with significant depressed mood, we suggest first-line therapy with an antidepressant (**Grade 2B**). Options include a serotonin-norepinephrine reuptake inhibitor (SNRI) such as duloxetine, a secondary tricyclic drug such as desipramine, or possibly bupropion, if the pain is complicated by fatigue or somnolence. (See 'Analgesic antidepressants' above.)

  For patients with neuropathic pain that is not associated with a depressed mood, we suggest first line therapy with gabapentin or pregabalin (**Grade 2C**). We generally prefer pregabalin because of simplified dosing. (See 'Gabapentin and pregabalin' above.)

  Given the positive placebo-controlled trial of duloxetine for painful taxane or platinum-induced neuropathy, duloxetine is an appropriate first-line agent in this setting. However, additional data will be needed to establish the superiority of duloxetine over an alpha-2-delta modulator in these patients, and the efficacy of duloxetine in patients with chemotherapy-induced peripheral neuropathy (CIPN) from other drugs such as vinca alkaloids. (See 'Antidepressants' above and "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Duloxetine and other antidepressants'.)

- For refractory cases, we suggest second-line therapy with the alternative agent, an antidepressant or an anticonvulsant, depending on which drug was used initially.

- A trial of another anticonvulsant, a cannabinoid (eg, dronabinol), or an alpha-2 adrenergic agonist (eg, tizanidine) could be considered in patients with neuropathic pain that is refractory to opioids and other appropriate adjuvant analgesics. (See 'Alpha-2 adrenergic agonists' above and 'Cannabis and cannabinoids' above and 'Other anticonvulsants' above.)

- A trial of a transdermal lidocaine patch could be considered in patients who have focal, peripherally-generated pain.

Bone pain — Patients with multifocal bone pain are usually managed with a non-steroidal antiinflammatory agent (NSAID), unless they have a specific contraindication to use of these agents, and an opioid, with or without an adjuvant analgesic used specifically for bone pain. (See "Cancer pain management: Use of acetaminophen and nonsteroidal antiinflammatory drugs", section on 'Indications and contraindications'.)

- We recommend the use of bisphosphonates in patients with symptomatic bone metastases from a variety of cancers (**Grade 1A**). Bisphosphonates prevent skeletal-related events; they may also improve pain. (See 'Osteoclast inhibitors' above.)

- Glucocorticoids may be useful in patients with opioid-refractory bone pain, especially in patients with advanced illness or a "pain crisis", which is defined as severe and escalating pain that is not responding sufficiently to an opioid. (See 'Choice of agent and dose' above.)

- The use of bone-targeted radioisotopes is typically reserved for the patient with multifocal bone pain that is refractory to other treatment, whose blood counts are not very low, and who is not expected to require myelosuppressive chemotherapy in the near future. (See 'Bone-targeted radioisotopes' above.)

Bowel obstruction — Medical management of patients with malignant bowel obstruction is focused on control of pain, distention, and vomiting using hydration, opioids, and adjuvant analgesics that may reduce symptoms by lessening peritumoral edema or diminishing intraluminal secretions and peristaltic movements.

- We suggest use of octreotide for the management of GI symptoms in patients with symptomatic inoperable bowel obstruction (**Grade 2B**). (See 'Drugs used for the pain of bowel obstruction' above.)
- In most cases, we use combination therapy rather than octreotide alone. This includes an opioid, an anticholinergic drug such as glycopyrrolate, and a low-dose glucocorticoid such as dexamethasone (1 to 2 mg once or twice daily) (see 'Drugs used for the pain of bowel obstruction' above).

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Topic 2815 Version 45.0

Cancer pain management: Adjuvant analgesics (coanalgesics)

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INTRODUCTION — Opioid therapy is the first-line approach for moderate or severe pain in populations with active cancer. However, the comprehensive management of pain in patients with cancer also requires expertise in the use of the nonopioid analgesics, such as acetaminophen (paracetamol), non-steroidal antiinflammatory agents (NSAIDs), and a group of drugs referred to as "adjuvant" analgesics or coanalgesics. Adjuvant analgesics are drugs that are marketed for indications other than pain, but are potentially useful as analgesics when added to opioid therapy in patients with chronic pain syndromes. (See "Cancer pain management with opioids: Optimizing analgesia" and "Cancer pain management: Use of acetaminophen and nonsteroidal antiinflammatory drugs".)

A stepwise approach to management of cancer pain that includes both opioid and nonopioid drugs has been codified in the World Health Organization's (WHO) "analgesic ladder" approach to cancer pain management (figure 1) [1]:

- Step 1, which represents mild to moderate cancer-related pain, suggests the use of acetaminophen or an NSAID, possibly combined with an adjuvant drug to provide additional analgesia, treat a side effect, or manage a coexisting symptom.
- For patients with moderate or severe pain, and those who do not achieve adequate relief with acetaminophen or an NSAID alone, treatment with a step 2 opioid (conventionally used for moderate pain) or a step 3 opioid (conventionally used for severe pain) is appropriate. On both steps 2 and 3, the use of an acetaminophen or an NSAID should be considered, as well as other drugs (adjuvants) to enhance analgesia or treat side effects.

The analgesic ladder approach is not an evidence-based guideline, but it provides a framework for the stepwise and systematic approach to managing cancer pain. (See "Cancer pain management: General principles and risk management for patients receiving opioids", section on 'General principles of pain management'.)

This topic review will cover the use of adjuvant analgesics in cancer pain management. Assessment of cancer pain, a review of specific cancer pain syndromes, the clinical use and side effects of opioid analgesics, use of acetaminophen and NSAIDs in patients with cancer pain, and non-pharmacologic methods of cancer pain management are covered elsewhere. (See appropriate topic reviews.)

DEFINITION OF AN ANALGESIC ADJUVANT — The term "adjuvant analgesic" was originally coined to refer to a small number of drugs that were marketed for indications other than pain, but were found to be potentially useful as analgesics in patients receiving opioid therapy. Over the past three decades, the number, diversity and uses of these drugs have increased dramatically, and several are now indicated as first-line therapy for certain types of pain [2]. As a result, the term "adjuvant analgesic" has become somewhat of a misnomer, but it is still commonly applied in the context of cancer pain. The term is used interchangeably with the term "coanalgesic".

Integration into cancer pain management — Adjuvant analgesics are often considered for treatment of chronic cancer pain when a patient is poorly responsive to opioids (ie, inability to titrate the opioid to a dose that maintains a favorable balance

between analgesia and side effects). The addition of an adjuvant analgesic is one approach among many that may be considered for such patients [3]. (See "Cancer pain management with opioids: Optimizing analgesia", section on 'Dose titration' and "Cancer pain management with opioids: Prevention and management of side effects".)

As a general rule, a trial of a coanalgesic in the setting of poor opioid responsiveness should usually be considered only after efforts have been made to optimize opioid therapy (ie, by adjusting the dose or, if indicated, rotating to a different opioid). Adding a second analgesic only after the opioid has been optimized ensures that the second drug is needed, reduces the risk of additive toxicity by eliminating the need to titrate both drugs simultaneously, and limits confusion in determining the source of an adverse drug effect should one arise. (See "Cancer pain management with opioids: Optimizing analgesia", section on 'Opioid poorly responsive pain'.)

Available agents — The large and growing number of adjuvant analgesics can be categorized on the basis of how they are used in clinical practice [2]. This information is evolving as new trials are conducted, clinical experience expands, and as treatments that were developed for populations with noncancer pain are extrapolated to the cancer population. Based upon conventional practice, the categories of available agents include (table 1 and table 2):

- Drugs potentially useful for any type of pain (multipurpose analgesics)
- Drugs used for treatment of neuropathic pain
- Drugs used for bone pain
- Drugs used for pain and other symptoms in the setting of bowel obstruction

MULTIPURPOSE ANALGESICS — Some drug classes have been studied in diverse types of chronic pain. The evidence of broad analgesic efficacy supports the view that the specific agents within these classes (including glucocorticoids, antidepressants, alpha-2 adrenergic agonists, cannabinoids, and topical therapies) function as multipurpose analgesics that have potential value for any type of chronic pain.

Glucocorticoids — In palliative care, glucocorticoids are often used to alleviate symptoms such as pain, nausea, fatigue, anorexia, and malaise, and improve overall quality of life. A large body of clinical experience suggests that glucocorticoids may be beneficial for a variety of types of pain, including neuropathic and bone pain, pain associated with capsular expansion or duct obstruction, pain from bowel obstruction, pain caused by lymphedema, and headache caused by increased intracranial pressure. However, the randomized trials that have been conducted to assess the analgesic properties of glucocorticoids have been small, and produced mixed results [4-10]; a year 2013 systematic review of four of these randomized trials [4,7-9] concluded that the quality of the evidence was low and that no conclusion could be reached about the analgesic benefits of glucocorticoids [11]. More recently, an analgesic benefit for the use of glucocorticoids in patients with advanced cancer using opioids could not be shown in a trial in which 50 patients with cancer receiving opioids whose pain intensity was ≥4 on a scale of 1 to 10 were randomly assigned to methylprednisolone 16 mg twice daily or placebo for seven days [10]. At the seven-day evaluation point, there were no differences in mean pain intensity or relative analgesic consumption, but patients using methylprednisolone had significant short-term improvements in fatigue, appetite loss, and patient satisfaction. However, it is difficult to conclude from this very small study that analgesic benefits are not produced by glucocorticoid therapy, particularly in specific subgroups of cancer patients. (See "Assessment of cancer pain", section on 'Nociceptive pain' and "Management of vasogenic edema in patients with primary and metastatic brain tumors" and "Treatment and prognosis of neoplastic epidural spinal cord compression, including cauda equina syndrome".)

Choice of agent and dose — Dexamethasone is usually preferred for the management of cancer-related pain, presumably because of its long half-life and relatively low mineralocorticoid effects (table 3). However, there is no empiric evidence that this drug is either safer or more effective in the cancer population than any other glucocorticoid. Prednisone and methylprednisolone are acceptable alternatives. (See "Pharmacologic use of glucocorticoids".)

A typical regimen for patients with cancer-related pain is 1 to 2 mg of dexamethasone orally or parenterally twice daily; this may be preceded by a larger loading dose of 10 to 20 mg. This regimen, or comparable regimens of alternative steroids, is based upon clinical experience and is not evidence-based. Patients may do well with lower or higher doses, or with once-daily rather than twice-daily dosing.

Regardless of the regimen that is selected, the intent is usually for ongoing chronic use in the setting of advanced illness. In this situation, the risk of long-term toxicity, which includes myopathy, immunocompromise, psychotomimetic effects, and

hypoadrenalism, is attenuated by limited life expectancy and the need to address the multiple sources of suffering. (See "Major side effects of systemic glucocorticoids".)

There are some situations for which a brief regimen of high-dose glucocorticoids might be selected. Originally developed for the treatment of emerging epidural spinal cord compression (including cauda equina syndrome), a brief period of high-dose glucocorticoids is appropriate for any "pain crisis", which is defined as severe and escalating pain that is not responding sufficiently to an opioid.

In such cases, a typical regimen consists of a dexamethasone loading dose of 50 to 100 mg intravenously, which may be followed by 12 to 24 mg four times daily; this dose is then tapered over one to three weeks, usually as some other intervention, such as radiotherapy or a pain intervention (eg, neural blockade), is used to treat the pain.

Although the high-dose regimen is administered with the expectation that it will provide more rapid and substantial pain relief than a lower dose regimen, the only evidence for this originates from populations with epidural spinal cord compression, and even these data are conflicting [12]. Both the limited evidence and the potential for dose-related toxicity (which is clearly higher with higher dose regimens) must be recognized in weighing the potential benefits of the high-dose approach. This subject is addressed in detail elsewhere. (See "Treatment and prognosis of neoplastic epidural spinal cord compression, including cauda equina syndrome", section on 'Clinical trials'.)

Analgesic antidepressants — Antidepressants have been widely studied in populations with chronic pain, and the available data suggest that these drugs act as multipurpose analgesics [2,13-16]. Although very few of these studies have included cancer patients, the utility of these drugs for treatment of cancer pain has been extrapolated from data in other conditions.

In opioid-treated populations with advanced medical illness, antidepressants have been predominantly used for neuropathic pain. However, given the range of their potential analgesic efficacy, they could be considered for other types of chronic pain as well. (See 'Drugs used for neuropathic pain' below and "Assessment of cancer pain", section on 'Neuropathic pain'.)

Mechanism of analgesic effect — Antidepressants function as primary analgesics. Although pain reduction may be enhanced if there is a positive mood effect, analgesia is not dependent on mood elevation and pain can be improved in euthymic patients. If a patient with chronic cancer pain has depressed mood, a relatively early trial of an analgesic antidepressant is appropriate in the hope of achieving a separate and positive effect on mood.

The primary analgesic mode of action is thought to be related to enhanced availability of monoamines at synapses within neural pathways that are part of the descending pain modulating system. Inhibition of norepinephrine reuptake appears to be the most important mode of action, but serotonergic and dopaminergic effects also may play a role in analgesia. (See "Definition and pathogenesis of chronic pain".)

Selection of agent and dose — The antidepressants comprise several subclasses and numerous drugs (table 1). Analgesic efficacy is best established for some of the tricyclic compounds [13,17-19] and the serotonin-norepinephrine reuptake inhibitors (SNRIs) [16,19-22]; there is minimal evidence of analgesic efficacy with the serotonin-selective reuptake inhibitors (SSRIs) [13,23,24]. Benefit has also been suggested for bupropion (a dopamine reuptake inhibitor) in patients with neuropathic pain [25,26].

The tricyclic antidepressants include tertiary amines, such as amitriptyline, and secondary amines, such as nortriptyline and desipramine. The secondary amines are more selective at noradrenergic reuptake sites, and they have a more favorable side effect profile than does amitriptyline. As a result, when a tricyclic is chosen in a medically ill patient, desipramine or nortriptyline is usually preferred. All of the tricyclic compounds are relatively contraindicated in patients with serious heart disease, severe prostatic hypertrophy, and narrow-angle glaucoma. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Side effects'.)

There is strong evidence that at least some of the SNRIs (which include duloxetine, milnacipran, venlafaxine, and desvenlafaxine) have analgesic effects. Evidence of analgesic efficacy is best described with duloxetine [21,22], but the literature lacks trials in patients with cancer pain, and there are no comparative trials within the SNRI class.

Overall, the side effect profile of the SNRIs (which includes nausea, sexual dysfunction, and somnolence or mental clouding) is favorable relative to desipramine and nortriptyline. There is a great deal of individual variation, however. Among patients with serious medical illness, such as those with cancer, the first-line analgesic antidepressants to consider should be either a

secondary amine tricyclic compound (usually desipramine) or a SNRI (usually duloxetine), and the decision between these drugs usually is based on a case-by-case assessment of risk and cost.

Other antidepressants are considered as second-line drugs, typically considered if the initial therapeutic attempt yields side effects or a limited analgesic response. The exception is bupropion, a dopamine and norepinephrine reuptake inhibitor that is distinguished by its tendency to be activating. Given this latter effect, a trial of bupropion sometimes is considered early if cancer pain is complicated by fatigue or somnolence, even though the evidence of analgesic efficacy is weak. Bupropion should be avoided in patients at risk for seizures.

All of the analgesic antidepressants should be started at a relatively low initial dose (table 2). The starting dose for a trial of desipramine, for example, is 10 to 25 mg at night. The dose should be increased no more quickly than every few days in the absence of satisfactory relief or side effects. If analgesia is going to occur at any given dose, it typically appears within a week (developing more rapidly than the antidepressant effects). (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Early improvement and response'.)

Most patients who experience pain relief with desipramine respond at a dose between 50 and 150 mg per day. However, the tricyclics may have a drug concentration-response relationship for analgesia [17], and if neither analgesia nor intolerable side effects occur, continued dose escalation is reasonable. At relatively high doses (ie, above 100 mg per day), the plasma drug concentration and an electrocardiogram (ECG) should be checked. Tricyclic antidepressants can prolong the QTc interval and predispose to cardiac arrhythmias. These drugs should be used cautiously when a patient has known heart disease or is receiving other drugs (including methadone) that can prolong the QT interval (table 4). (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Plasma levels and therapeutic response' and "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects", section on 'Cardiac evaluation'.)

Other antidepressants such as duloxetine or bupropion should similarly be started at a relatively low initial dose (table 2), and titrated to conventional maximal doses to determine whether an analgesic or positive mood effect occurs. Unlike the tricyclics, these drugs do not prolong the QTc interval. However, gastrointestinal side effects (including nausea, dry mouth, and constipation) are common with duloxetine, and bupropion causes jitteriness or headache as relatively common initial side effects.

If possible, it is preferable to taper these drugs prior to discontinuation.

Other multipurpose analgesics — There are far fewer data supporting the use of the alpha-2 adrenergic agonists, cannabinoids, and topical therapies as multipurpose analgesics for the treatment of cancer pain.

Alpha-2 adrenergic agonists — Classification of alpha-2 adrenergic agonists such as clonidine and tizanidine as multipurpose analgesics is supported by both animal and human studies. Clonidine, which can be administered orally, transdermally, or intraspinally, has been mainly studied in patients with noncancer-related chronic pain. Spinally-administered clonidine has analgesic properties in patients with cancer pain and is more efficacious for neuropathic than nociceptive pain [27]. (See "Cancer pain management: Interventional therapies".)

There is less evidence of analgesic efficacy with tizanidine, an orally active centrally acting alpha-2 agonist that is approved as an antispasticity agent [28], or the parenteral alpha-2 agonist dexmedetomidine [29,30]. However, this class of drugs can provide analgesia in diverse types of pain. Although the mechanism is unknown, the analgesic effects presumably relate to increased activity in monoamine-dependent, endogenous pain modulating pathways in the spinal cord and brain.

The alpha-2 agonists produce somnolence and dry mouth, and may cause hypotension, which is usually orthostatic. This potential, combined with analgesic efficacy that appears to be lower than with other multipurpose drugs, indicates a limited role for these drugs in the medically ill.

Tizanidine has less hypotensive effect than clonidine and could be considered for a trial in patients with opioid-refractory neuropathic pain. Patients who are hemodynamically unstable, predisposed to serious hypotension (eg, by autonomic neuropathy, intravascular volume depletion, or concurrent therapy with potent hypotensive agents), or encephalopathic from other causes are not appropriate candidates. Dosing with tizanidine may be initiated just at bedtime in an effort to provide hypnotic effects. If the drug is tolerated, dose escalation using two divided daily doses is typically used when the intent of therapy is analgesia.

Cannabis and cannabinoids — Cannabinoids are derived from the cannabis (marijuana) plant, which contains over 400 compounds, including more than 60 cannabinoids. The primary psychoactive cannabinoid is delta-9-tetrahydrocannabinol (THC, also known as dronabinol). In vivo, cannabinoid molecules such as THC interact with an endogenous system that includes cannabinoid-like ligands (the endocannabinoids) as well as multiple receptors in both the periphery and central nervous system. (See "Cannabis use disorder: Epidemiology, comorbidity, and pathogenesis".)

Although concern about the abuse potential of cannabinoid drugs has slowed their development, several cannabinoid-type drugs are commercially available, and others are under study. The available data suggest that these compounds may be useful as multipurpose analgesics in palliative care populations [31-35], although few studies have been conducted in cancer patients [36].

An oromucosal spray containing THC plus cannabidiol (and smaller concentrations of other compounds), nabiximols (Sativex), is approved in Canada and elsewhere (but not yet in the United States) for treatment of neuropathic pain due to multiple sclerosis and as an adjunctive treatment for pain in patients with advanced cancer [37]. It is rapidly absorbed from the buccal mucosa, and the dose can be self-titrated by the patient.

The benefit of nabiximols for management of cancer pain was shown in a double-blind trial in which 177 cancer patients with inadequate analgesia despite chronic opioid dosing were randomly assigned to nabiximols (n = 60), THC alone (n = 58), or placebo (n = 59) for two weeks; doses were self titrated (with maximum permitted doses) until satisfactory relief or untoward side effects [34]. By the end of the study period, compared to placebo, the adjusted mean reduction in pain score from baseline was significantly higher with nabiximols, but not with THC alone. In addition, there was a nonsignificant trend toward fewer daily doses of all breakthrough medications in the nabiximols group, compared to placebo. However, there were imbalances in the baseline opioid dose that could have biased the results in favor of nabiximols. There was no evidence of loss of effect for the relief of cancer pain with long-term use of nabiximols [38].

Until newer cannabinoid preparations such as nabiximols become available in the US, clinical use of cannabinoids for cancer pain is limited to those agents that are marketed for purposes other than pain, including THC and nabilone. A trial of one of these drugs is usually considered only in those patients who are refractory to opioids and other appropriate adjuvant analgesics; most will have neuropathic pain. Nabilone should be started at 0.5 to 1 mg at night and titrated up to 3 mg twice daily, or higher if tolerated. Dronabinol usually is started at a dose of 2.5 mg once or twice daily, and titrated.

The most common side effects associated with the cannabinoids are dizziness, somnolence, and dry mouth.

The use of medical marijuana for refractory cancer pain is very controversial. Medical use of marijuana is legal in several countries, including the Netherlands and Canada. However, despite legalization by several states, marijuana use is still illegal in the United States at the federal level (which considers marijuana a schedule I controlled substance), and individuals prescribing or using marijuana for medical use are at risk for prosecution [39].

Although severe or chronic pain accounts for over 90 percent of the qualifying conditions for use of medicinal marijuana among registered users in several states in which it is legal [40-43], there are no controlled studies demonstrating the efficacy of inhaled marijuana as an adjunct to traditional pain medications for patients with cancer-related pain. Particularly in view of concerns for increased rates of respiratory infections and pneumonia among cannabis smokers and uncertainty about higher cancer rates in this population as well [36,44,45], its use cannot be recommended.

Topical therapies — Topical therapies have the potential to deliver analgesic compounds directly to the site that is presumably responsible, at least in part, for the persistent pain. The relative lack of systemic toxicity offers a therapeutic advantage that may be particularly relevant to the medically ill. Although topical analgesics have been used mostly for neuropathic pain, they have the potential for broader application. An overview of topical analgesics for treatment of superficial painful conditions is provided in the table (table 5).

Lidocaine — The most widely used topical therapies for pain contain local anesthetics. Lidocaine 5 percent transdermal patches are widely used for the treatment of focal and/or regional pain of all types. The evidence to support benefit is relatively weak, and consists of small, short-term, open-label nonrandomized studies that were conducted in patients with postherpetic neuralgia [46], and other noncancer disorders causing chronic pain [47,48]. Although the current approved use (based on clinical trials) is a 12 hour per day dosing regimen, some patients find that pain relief does not last 24 hours and continuous

application is common in the clinical setting. Multiple patches are often used together. There are limited data that indicate a high level of safety with four patches applied for 24 hours a day for up to 72 hours [49].

The most frequently reported adverse event is mild to moderate skin irritation at the patch application site, which seems to be related to the vehicle rather than to lidocaine. There is only a remote risk of toxicity from systemic absorption of lidocaine. Cost may be prohibitive.

Other local anesthetics — Topical analgesia also may be possible using creams or gels containing local anesthetics:

- A commercially available mixture of prilocaine and lidocaine, known as eutectic mixture of local anesthetics (EMLA) cream, is capable of penetrating the skin and producing a dense local cutaneous anesthesia [50]. This product and others have been approved to prevent the pain of needle puncture or incision. In cancer patients with a peripheral source of pain, application of a thin layer under an occlusive dressing has been used as an adjunct to chronic therapy. The treatment is relatively expensive and difficult to sustain for long periods.
- Surveys of studies using relatively high concentrations of topical lidocaine gel suggest that a compound of this type can produce similar benefits for focal, peripherally-generated pain [51]. Although there is a remote risk of toxicity from systemic absorption, the safety of the lidocaine patch or compounded creams suggest that a trial should be considered in patients who have pain that is localized to a relatively small area.
- Capsaicin, the naturally occurring constituent of the chili pepper, depletes substance P from the terminals of afferent C-fibers. Topical application of a commercially available capsaicin cream or low-dose transdermal patch (which are available over the counter in the US) or a single application of a high-dose patch (8 percent capsaicin, Qutenza, which requires a prescription, (table 5)) has yielded weak to moderate analgesic effects in controlled trials focusing on patients with various types of neuropathic and joint pain [52-54]. Burning at the application site, which is often transitory, is the major side effect and may be limiting. Application three to four times daily for a period of at least a week is needed to determine benefit.

Antiinflammatory and antidepressant drugs — Numerous anti-inflammatory drugs have been investigated for topical use; diclofenac patch, cream, and gel are commercially available in the US; others are available outside of the US (table 5).

Like capsaicin, there is some evidence that diverse types of pain may respond favorably. Although data from controlled trials in populations with musculoskeletal pain are conflicting [55,56], there is sufficient evidence of effectiveness and safety to warrant a therapeutic trial in patients with small areas of pain related to neuropathic or nociceptive mechanisms. (See "Assessment of cancer pain", section on 'Inferred pathophysiology (types of cancer pain)'.)

Evidence for the analgesic efficacy of topical tricyclic antidepressants is conflicting [57], but a cream containing doxepin is commercially available and approved for the short-term management of pruritus. Given the safety of this approach, a trial of topical doxepin may be considered for the patient with local or regional pain. (See "Pruritus: Overview of management".)

Other drugs have been used empirically in specially compounded creams for use in patients with pain. The most popular are ketamine and gabapentin, but a variety of others are in use. Supporting data are very meager or absent, but given the relative safety of topical application of these agents, a clinical trial may be reasonable. Cost must be considered when recommending these strategies.

DRUGS USED FOR NEUROPATHIC PAIN — All of the drugs classified as multipurpose analgesics may be considered for a clinical trial in patients with opioid-refractory neuropathic cancer pain. However, the most important of the multipurpose adjuvant analgesics for treatment of neuropathic pain are the analgesic antidepressants and anticonvulsants.

Anticonvulsant analgesics — The anticonvulsants represent a diverse group of drugs that vary in mechanisms and clinical effects (table 1 and table 2). Analgesic effects are best characterized for gabapentin and pregabalin, two drugs that are now considered the first-line approach for patients without comorbid depression who have non-chemotherapy-related neuropathic cancer pain that is refractory to opioid analgesics [58].

Gabapentin and pregabalin — Gabapentin and pregabalin have been extensively studied in diverse types of neuropathic pain, particularly postherpetic neuralgia and painful diabetic neuropathy [59-66]. Fewer data are available in patients with neuropathic pain related to cancer or its treatment [60,67-72]:

- In two randomized placebo-controlled trials involving populations of opioid-treated patients with cancer-related neuropathic pain, gabapentin and pregabalin were each significantly better than placebo in improving neuropathic pain and dysesthesias [60,67]; one of these trials directly compared gabapentin and pregabalin, and is discussed in more detail below [67].
- On the other hand, another randomized trial of gabapentin versus placebo for chemotherapy-induced painful peripheral neuropathy failed to show any benefit for gabapentin. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Anticonvulsants'.)
- A systematic review of the effectiveness of antiepileptic drugs or antidepressants added to opioids for neuropathic pain from cancer concluded that benefit from any adjuvant was modest and much less than that seen in patients with noncancer neuropathic pain, strongest for gabapentin, and counterbalanced by an increase in adverse events [73].
- In contrast, a second systematic literature review of the evidence for pharmacologic treatment of neuropathic cancer pain concluded that the absolute risk benefit for all agents (antidepressants, anticonvulsants) greatly outweighed the absolute risk for harm, but that all studies had low methodologic quality that precluded drawing conclusions about the relative effect sizes of the different medication groups [74].

Gabapentin and pregabalin both act by binding to the alpha-2 delta protein modulator of the N-type, voltage-gated calcium channel. Binding to this protein reduces calcium influx into the neuron, and lessens the likelihood of depolarization.

Unlike all other anticonvulsants, gabapentin and pregabalin are not metabolized in the liver and they have no known drug-drug interactions. Both drugs are excreted by the kidneys, which necessitates dose reduction in the setting of renal impairment. Their main side effects are mental clouding, dizziness, and somnolence; edema and weight gain are less common.

The main difference between gabapentin and pregabalin is pharmacokinetic. Absorption and entry of gabapentin into the central nervous system (CNS) is facilitated by a saturable transporter in the small bowel and CNS. At relatively higher doses (approximately 1800 mg per day, but could be higher or lower in individual cases, (table 2)), the kinetics become nonlinear and there is less complete absorption with each dose increment. These saturable kinetics mean that gabapentin has a pharmacokinetic "ceiling", which coexists with a possible pharmacodynamic "ceiling" of the type that is observed with all adjuvant analgesics (ie, at some point, a maximum effect is reached even if the plasma concentration of the drug is further increased).

In contrast, absorption of pregabalin is not dependent on a saturable transport mechanism, and this drug only has the unpredictable pharmacodynamic ceiling. This linear pharmacokinetic profile simplifies dosing of pregabalin compared to gabapentin.

Whether either drug is superior to the other for treatment of neuropathic pain is unclear. A double-blind trial randomly assigned 120 patients with cancer and severe neuropathic pain to gabapentin (900 mg daily for one week followed by 1200 mg daily for one week, then 1800 mg daily), pregabalin (150 mg daily for one week, followed by 300 mg daily for one week, then 600 mg daily), amitriptyline (50 mg daily for one week followed by 75 mg per day for one week, then 100 mg daily at bedtime), or placebo [67]. The primary outcome measure was global intensity of pain, as measured on a 100 mm Visual Analog Scale (VAS). By week four, the mean VAS score with pregabalin was significantly less than that of the patients receiving gabapentin, and the percentage of patients requiring rescue morphine in the placebo, amitriptyline, gabapentin, and pregabalin groups was significantly different (100, 57, 33, and 17 percent, respectively).

This study suggests that pregabalin may have superior efficacy but the limitations of the study (no indication of how randomization or blinding was performed, no power analysis, and the primary endpoint analysis was not an "intention to treat" analysis) preclude definitive conclusions. In addition, the drugs were tested at doses that may not be fairly compared; the initial dose of pregabalin was relatively high while the top dose of gabapentin was the minimum dose that is often chosen. For all of these reasons, it cannot be concluded that pregabalin is superior to gabapentin for treatment of neuropathic pain.

The starting dose of pregabalin is usually 50 to 75 mg per day in two divided doses (a lower dose should be used in the medically frail), and escalation to the usual effective dose of 150 to 300 mg twice daily typically is accomplished in two to three steps over one week. In the medically frail cancer patient, gabapentin is often initiated at a dose of approximately 100 to 300 mg per day (one-half the dose of a non-frail patient). The dose is gradually escalated every few days while monitoring

analgesia and side effects. If pain relief does not occur, in the absence of an analgesic ceiling or adverse effects, dose escalation can extend to 3600 mg per day administered in two to three divided doses and sometimes higher.

Controlled trials of pregabalin that have included "gabapentin failures" have shown that patients may respond to pregabalin even if gabapentin was not tolerated [69]. Given these data and extensive clinical observations, it is appropriate to consider a trial of the alternate drug if an attempt with the first does not yield benefit.

If possible, it is preferable to taper these drugs prior to discontinuation.

Other anticonvulsants — Numerous other anticonvulsants have been studied as analgesics [75]. Older anticonvulsant such as carbamazepine, valproate, and phenytoin are perceived as having potential analgesic effects based on trials performed several decades ago [76]. Carbamazepine remains a preferred drug for trigeminal neuralgia, but in the cancer population, it is seldom used because of the risk of leucopenia and the need for monitoring myelosuppressive effects. (See "Trigeminal neuralgia".)

The data supporting the analgesic efficacy of valproate and phenytoin are limited. Although these drugs may be considered for trials in patients with intractable neuropathic pain, conventional practice in countries that have access to newer agents relegates them to trials after other anticonvulsants have been demonstrated to be ineffective.

Lamotrigine has been effective in studies of central pain, trigeminal neuralgia, and painful HIV polyneuropathy [62], but it has not been analgesic in other trials, including one conducted in patients with chemotherapy induced painful peripheral neuropathy [77]. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Anticonvulsants'.)

Lamotrigine is associated with a small risk of severe cutaneous hypersensitivity, which is relatively higher in younger patients. The drug should not be used in patients under the age of 15, and slow titration of the dose from a low initial dose is necessary to reduce the risk of hypersensitivity.

The need for this slow initial titration, which ideally requires more than one month to reach a dose that might be effective, as well as the risk of Stevens-Johnson syndrome, diminishes enthusiasm for an early trial of lamotrigine. Typically, it is considered only after trials of several preferred drugs for neuropathic pain have been ineffective.

Oxcarbazepine is a metabolite of carbamazepine, which has similar anticonvulsant properties and a safer pharmacologic profile. Although studies have not been uniformly positive, it has been shown to be analgesic in trigeminal neuralgia and several other types of neuropathic pain [78]. Like lamotrigine, a trial may be considered after trials of the alpha-2-delta modulators and perhaps one or two of the analgesic antidepressants have proved to be ineffective.

Other anticonvulsants may be considered for treatment-refractory cancer-related neuropathic pain [2,75]:

- Topiramate, an effective drug for migraine, has been variably effective in studies of neuropathic pain, but anecdotal experience suggests that some patients respond and derive substantial benefit [79].
- There are conflicting reports on the analgesic efficacy of levetiracetam, zonisamide, and tiagabine, and in the absence of additional data, these drugs usually are not considered unless others are not available.
- Clonazepam is a benzodiazepine. Very meager data support analgesic efficacy in patients with neuropathic pain [80]; its anxiolytic effects may be favorable, however, and a trial often is considered in the patient with refractory neuropathic pain associated with anxiety.
- Lacosamide, a relatively new anticonvulsant, is a sodium channel modulator, a unique mechanism of action. Large controlled trials in patients with painful diabetic neuropathy suggest benefit [81], although there are no data in patients with cancer-related pain. This agent could be considered among those that are potentially useful for treatment of refractory neuropathic pain.

None of these agents has been studied in patients with chemotherapy-induced peripheral neuropathy. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Pharmacologic agents'.)

Antidepressants — As described previously, the most useful of the analgesic antidepressants are the serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine, and the secondary amine tricyclic compounds (eg,

desipramine). Evidence of analgesic efficacy for chronic pain has been demonstrated in randomized controlled trials and meta-analyses. (See 'Analgesic antidepressants' above.)

Although trials comparing antidepressants versus other strategies (such as anticonvulsants) for treatment of neuropathic pain are lacking, most experts consider these drugs to represent preferred first-line treatments for neuropathic pain that is associated with significant depressed mood, and appropriate second-line agents (after the alpha-2-delta modulators gabapentin or pregabalin, see below) for non-depressed patients who have neuropathic pain [58]. (See 'Analgesic antidepressants' above.)

The systematic review of the effectiveness of antiepileptic drugs or antidepressants added to opioids for neuropathic pain from cancer described above concluded that benefit from any adjuvant was modest and much less than that seen in patients with noncancer neuropathic pain, strongest for gabapentin, and counterbalanced by an increase in adverse events [73].

A second systematic literature review of the evidence for pharmacologic treatment of neuropathic cancer pain concluded that the absolute risk benefit for all adjuvant analgesics, including antidepressants, greatly outweighed the absolute risk for harm, but that all studies had low methodologic quality that precluded drawing conclusions about the relative effect sizes of antidepressants relative to any other medication groups [74].

However, positive results with duloxetine in a single randomized, double-blind placebo-controlled crossover trial conducted in patients with painful chemotherapy induced peripheral neuropathy after treatment with taxanes or platinum-containing chemotherapy supports the view that in this setting, duloxetine is an appropriate first-line agent, particularly in view of a negative gabapentin trial. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Duloxetine and other antidepressants' and "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Anticonvulsants'.)

However, additional data will be needed to establish the superiority of duloxetine or any other antidepressant over an alpha-2-delta modulator in these patients. (See 'Gabapentin and pregabalin' above.)

Other drugs used for neuropathic pain — Other drug classes play a far less prominent role in the clinical strategy for cancer-related neuropathic pain. Nonetheless, occasional patients with refractory neuropathic pain may be candidates for a trial of one or more of these uncommon treatments.

Other multipurpose analgesics — Among the drug classes used less often are those previously grouped with the multipurpose analgesics. A trial of an alpha-2 agonist such as tizanidine, or a trial of a cannabinoid such as dronabinol, might be considered in refractory cases of neuropathic pain. (See 'Alpha-2 adrenergic agonists' above and 'Cannabis and cannabinoids' above.)

Topical analgesics — Topical agents, usually a local anesthetic, may also be considered for an early trial when neuropathic pain is focal or regional and opioid therapy is not sufficient. At least one trial suggests potential benefit for a topical gel containing baclofen, amitriptyline, and ketamine in patients with painful chemotherapy induced peripheral neuropathy. (See 'Topical therapies' above and "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Topical treatments containing amitriptyline and ketamine with and without baclofen'.)

Sodium channel blockers — Blockade of sodium channels has been recognized as an analgesic mechanism for decades and the potential role of the new sodium channel modulator, lacosamide, was mentioned above (see 'Other anticonvulsants' above).

Treatment approaches using older sodium channel blockers include oral therapy with antiarrhythmic drugs, such as mexiletine or tocainide, or parenteral therapy, usually with lidocaine. A brief intravenous infusion of lidocaine, typically 2 to 4 mg/kg infused over 20 to 30 minutes in a monitored setting, can be extremely useful in the management of severe neuropathic pain, resulting in prompt pain reduction so that other strategies can be implemented more gradually. The analgesic effects and generally favorable safety profile of these drugs are strongly supported by the literature [82,83]; the usual side effects are dizziness, nausea, and fatigue.

Ketamine and other NMDA receptor antagonists — The N-methyl-D-aspartate (NMDA) receptor is involved in both the sensitization of central neurons and the functioning of the opioid receptor, and there is good evidence that one of the commercially available NMDA receptor antagonists, ketamine, has analgesic properties [84]. At subanesthetic doses, ketamine

may be used as a brief infusion for treatment of severe refractory pain [85,86], as a more prolonged infusion (typically at the end of life), or as oral therapy [87]. The evidence to support benefit of ketamine as an adjuvant to opioid therapy is quite limited. In all, five randomized trials have been conducted:

Three small trials conducted in 1996, 1999 and 2000 suggested enhanced control of cancer pain when ketamine was given with morphine [88-90] Three later randomized trials, one conducted in 20 patients with refractory cancer pain, one in 30 patients receiving morphine for treatment of cancer pain, and another in 185 patients with refractory chronic pain related to cancer or its treatment, failed to demonstrate any benefit from the addition of infusional or oral ketamine to opioids [91-93]. In the largest of the three trials, only 39 of the original 93 patients allocated to ketamine received the full five days of planned treatment, with approximately equal numbers discontinuing therapy for lack of efficacy and treatment-related toxicity (somnolence, constipation, nausea/vomiting, dizziness, cognitive disturbance) [92]. Only 35 of the original 91 patients assigned to placebo received the full five days of planned treatment, but nearly all of the dropouts were for treatment failure. A 2012 Cochrane review [94] of two of these randomized trials [88,90] (the rest were excluded because of methodologic problems or extremely small number of patients completing the study) concluded that the evidence was insufficient to assess the effectiveness of ketamine in this setting.

Nevertheless, this approach continues to be used by experienced pain clinicians, particularly in the setting of otherwise refractory neuropathic pain at the end of life, based mainly upon favorable anecdotal experience [85,86]. The side effect profile of ketamine, including particularly psychotomimetic effects and delirium, is problematic, however; and as a result, the most common use is short-term therapy in a monitored setting. Based upon anecdotal observations that treatment with a benzodiazepine, such as lorazepam, or a neuroleptic, such as haloperidol, reduces the risk of psychotomimetic effects from ketamine, most practitioners co-administer one of these drugs prior to the start of the infusion and repeatedly during longer term treatment; a benzodiazepine usually is preferred [95]. Gradual dose titration of the ketamine may also reduce the incidence of psychotomimetic effects [96].

Other NMDA receptor antagonists, such as memantine, amantadine and dextromethorphan, have been studied in neuropathic pain states, with mixed results [97]. They are rarely considered for trials in cancer-related neuropathic pain that has not responded to other agents.

GABA receptor inhibitors and agonists — Among the gamma aminobutyric acid (GABA) receptor inhibitors are the benzodiazepines, which affect the GABAA receptor subtype, and baclofen, which affects the GABAB subtype. As noted previously, the only benzodiazepine that is typically used for neuropathic pain is clonazepam. (See 'Other anticonvulsants' above.)

Baclofen, a selective GABAB agonist, is an antispasticity drug with established efficacy in trigeminal neuralgia. It has been used anecdotally for neuropathic pain of other types, including cancer pain [98]. A low starting dose of 5 mg twice daily can be gradually escalated to doses that may exceed 200 mg per day in some patients.

SUMMARY AND RECOMMENDATIONS OF EXPERT GROUPS — Opioids are widely used for treatment of cancer pain because of their safety, ease of titration, reliability, and effectiveness for all types of pain, including neuropathic pain. Although neuropathic pain may be more difficult to treat, a favorable response to opioid-based analgesia is often possible. (See "Assessment of cancer pain" and "Cancer pain management with opioids: Optimizing analgesia".)

For this reason, some experts advocate a trial of an adjuvant analgesic for cancer-related neuropathic cancer pain only in the setting of relatively poor opioid responsiveness, ie, after an opioid has been titrated to optimize the balance between analgesia and side effects. This view is somewhat controversial, however, and others advocate early use of adjuvant analgesics, usually in tandem with cautious opioid titration.

Experts generally agree that this first-line or concurrent use of an opioid should be considered only in patients with active cancer; patients with no active disease (such as those with posttreatment neuropathic pain like a postmastectomy pain syndrome) are usually similar to patients with neuropathic pain that is not cancer-related. In these situations, opioid therapy is usually perceived to have a more limited role. The choice of therapy may also be influenced by the type of neuropathic pain. For example, guidelines from the American Society of Clinical Oncology recommend duloxetine for initial treatment of chemotherapy-induced painful peripheral neuropathy. (See "Prevention and treatment of chemotherapy-induced peripheral

neuropathy", section on 'Recommendations of expert groups' and "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Duloxetine and other antidepressants'.)

Given the weight of evidence, we consider analgesic antidepressants such as SNRIs or tricyclics to represent first-line treatments for neuropathic pain that is associated with significant depressed mood, and second-line (after the alpha-2-delta modulators gabapentin or pregabalin) in non-depressed patients who have neuropathic cancer pain that is refractory to opioid therapy. Given the positive duloxetine trial, and negative trials of gabapentin and other anticonvulsants as well as tricyclic antidepressants in patients with painful chemotherapy-induced peripheral neuropathy, we prefer duloxetine in this setting. (See "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Pharmacologic agents'.)

Guidelines for treatment of neuropathic pain from the International Association for the Study of Pain (IASP) focus on noncancer pain populations, and recommend first-line use of selected anticonvulsants (specifically gabapentin or pregabalin) or an analgesic antidepressant (either a secondary amine tricyclic antidepressant such as nortriptyline or desipramine or an SNRI such as duloxetine or venlafaxine) [58]. An analgesic antidepressant should be tried initially if the patient has a depressed mood. The guidelines indicate that opioid analgesics either alone or in combination with an analgesic adjuvant should be considered for patients with neuropathic cancer pain, as well as for episodic exacerbations of severe pain, or when prompt pain relief during titration of an adjuvant analgesic is needed.

Guidelines from the National Comprehensive Cancer Network (NCCN) and the European Association for Palliative Care [99] broadly concur with the IASP guidelines, suggesting that antidepressants or anticonvulsants are preferred first-line coanalgesics for the treatment of cancer-related neuropathic pain in patients whose pain is only partially responsive to opioids.

A stepwise approach to assessment and treatment is recommended in the IASP guidelines and is relevant to neuropathic cancer pain [58]:

- Assessment of the pain and establishment of the likely neuropathic etiology. The assessment should also include identification of relevant comorbidities which may be impacted by treatment of neuropathic pain, or require modifications in the initial treatment regimen. (See "Assessment of cancer pain".)
- Initiate antineoplastic therapy for the disease causing the neuropathy, if applicable.
- Initiate symptom treatment for the painful neuropathy.

ADJUVANT DRUGS USED FOR BONE PAIN — The assessment of a patient with new bone pain may suggest the need for radiation therapy or an intervention such as kyphoplasty or surgery. (See "Assessment of cancer pain" and "Radiation therapy for the management of painful bone metastases" and "Evaluation and management of complete and impending pathologic fractures in patients with metastatic bone disease, multiple myeloma, and lymphoma".)

Patients with multifocal pain usually are managed with a non-steroidal antiinflammatory agent (NSAID), unless they have a specific contraindication to use of these agents, and an opioid, with or without an adjuvant analgesic used specifically for bone pain. (See "Cancer pain management: Use of acetaminophen and nonsteroidal antiinflammatory drugs", section on 'Indications and contraindications'.)

In addition to a glucocorticoid, such as dexamethasone, drugs to consider in this setting include bisphosphonates, calcitonin, and bone-seeking radionuclides (table 1).

Osteoclast inhibitors

Bisphosphonates — For patients with metastatic bone disease, bisphosphonates prevent skeletal-related events, including fracture, and they may also improve pain and quality of life. Bisphosphonates act by directly inhibiting osteoclast activity, stimulating osteoblasts to produce osteoclast-inhibiting factor, and causing osteoclast apoptosis.

There are substantial data supporting the analgesic potential of all of the parenteral bisphosphonates, including pamidronate, zoledronic acid, ibandronate, and clodronate (not available in the US), as well as oral ibandronate and clodronate. In a Cochrane review, a significant improvement in bone pain was reported after receiving a bisphosphonate in patients with bone metastases from breast cancer in 6 of 11 studies [100]. (See "Osteoclast inhibitors in the management of bone metastases from breast cancer", section on 'Bisphosphonates'.)

Comparative data are very limited, and the specific drug is chosen on the basis of experience, cost and convenience. This subject is addressed in more detail elsewhere. (See "Bisphosphonates and denosumab in patients with metastatic cancer".)

Although generally well tolerated, the bisphosphonates are associated with some side effects (see "Risks of therapy with bone modifying agents in patients with advanced malignancy"):

- These drugs can impair renal function, but this is usually a transitory problem. Renal function should be checked prior to treatment, and if impaired, the starting dose should be lowered and the patient carefully monitored. Severe renal insufficiency is a relative contraindication to therapy.
- A temporary flu-like syndrome with fever and body aches commonly follows treatment initiation. Treatment with acetaminophen may be helpful.
- Hypocalcemia is possible when these drugs are administered even to normocalcemic patients. These patients usually are subsequently found to be vitamin D deficient. The calcium level should therefore be monitored during therapy.
- An unusual complication, osteonecrosis of the jaw, is characterized by painful erosions, ulcers, and sinus tracts in the mandible, and occasionally, the maxilla. This complication usually occurs after months of treatment and may be relatively more common during therapy with pamidronate and zoledronic acid than with other bisphosphonates; it is rare during oral therapy. Given the evidence that oral trauma and dental infections increase the risk of this complication, patients with bone pain and very poor dentition, jaw infection, or recent substantial dental procedures should be considered for an alternative pharmacologic strategy. (See "Risks of therapy with bone modifying agents in patients with advanced malignancy", section on 'Osteonecrosis of the jaw'.)

Denosumab — Osteoclast inhibition can also be achieved by targeting receptor activator of nuclear factor kappa B ligand (RANKL), a key component in the pathway for osteoclast formation and activation. Denosumab, a monoclonal antibody targeting RANKL, has been compared to zoledronic acid in patients with metastatic bone disease from a variety of solid tumors; all have concluded that there is a slight benefit to denosumab in terms of preventing skeletal-related events, but only one of the trials has reported endpoints related to bone pain [101]. In this trial comparing zoledronic acid versus denosumab in 2046 patients with advanced breast cancer and bone metastases, 43 percent of patients reported moderate to severe pain at baseline, although only approximately 16 percent were using strong opioids. Compared with the zoledronic acid group, fewer patients receiving denosumab who had no or mild pain at baseline progressed to moderate or severe pain (although the absolute difference was only 5 percent), there was an almost four month longer delay in the median time to pain worsening to moderate or severe, and fewer shifted from no or low analgesic use to strong analgesic use. However, palliation of pain severity as measured by the proportion of patients with meaningful improvement in pain (defined as a decrease of ≥2 points in the worst pain score), median time to meaningful improvement in worst pain score, and the time to decreased pain interference, was similar for both treatment groups. Thus, the analgesic superiority of denosumab relative to that of bisphosphonates for patients with painful bone metastases is not yet established. (See "Bisphosphonates and denosumab in patients with metastatic cancer" and "Bone metastases in advanced prostate cancer: Management" and "Overview of the use of osteoclast inhibitors in early breast cancer".)

Calcitonin — Small controlled trials have yielded conflicting information about the potential for subcutaneous calcitonin to reduce metastatic bone pain [102]. Given the lack of consistent evidence, this treatment generally is not recommended, although an empirical trial could be considered when other treatments are unavailable or ineffective.

Bone-targeted radioisotopes — Bone-seeking radioisotopes, such as strontium-89 and samarium-153, link a short-lived radiation source to a bisphosphonate molecule. Once injected, the drug is taken up at the site of bone metastases, and delivers radiation focally.

Although bone-targeted radioisotopes can be a useful treatment for multifocal bone pain, myelosuppression is a significant concern (although less with samarium than with strontium), and treatment requires special skills and facilities. If available, this approach is typically considered for the patient with refractory multifocal bone pain, whose blood counts are not very low, and who is not expected to require myelosuppressive chemotherapy in the near future.

These agents have been used most often for men with metastatic prostate cancer; their use is discussed in more detail elsewhere. (See "Bone metastases in advanced prostate cancer: Management", section on 'Bone-targeted radiopharmaceuticals'.)

DRUGS USED FOR THE PAIN OF BOWEL OBSTRUCTION — Bowel obstruction is a well-recognized complication in patients with advanced intraabdominal or pelvic tumors. Most of these patients are inoperable, and their survival is generally short. Some cases may be amenable to placement of a self-expanding metal stent [103]. (See "Enteral stents for the management of malignant colorectal obstruction".)

For patients with inoperable intestinal obstruction who are not appropriate for a stent, management with IV fluids and placement of a nasogastric tube for decompression has been the conventional approach historically. Decompression of gastric contents can also be achieved by placement of a percutaneous gastrostomy tube. However, these procedures provide only incomplete relief of distressing symptoms, and the ongoing presence of these tubes can be uncomfortable and distressing for the patient and his or her family.

More recently, medical management of inoperable patients has focused on adequate control of pain, distention, and vomiting using hydration, opioids, and adjuvant analgesics that may reduce symptoms by lessening peritumoral edema (glucocorticoids) and diminishing intraluminal secretions and peristaltic movements (anticholinergic agents and octreotide). Anticholinergic drugs (scopolamine, glycopyrrolate) and octreotide both reduce propulsive as well as nonpropulsive gut motility, and they decrease intraluminal secretions.

This subject is discussed in detail elsewhere. (See "Palliative care: Assessment and management of nausea and vomiting", section on 'Gastrointestinal obstruction'.)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword (s) of interest.)

- Basics topics (see "Patient information: Managing pain when you have cancer (The Basics)")

SUMMARY AND RECOMMENDATIONS — Adjuvant analgesics (coanalgesics) are drugs that were originally marketed for indications other than pain but are potentially useful as analgesics. Many of these drugs are useful for treatment of chronic cancer pain, and in those with active disease, usually are considered when a patient is poorly responsive to opioids. (See 'Definition of an analgesic adjuvant' above.)

The available agents are categorized on the basis of how they are used in clinical practice (table 1). (See 'Available agents' above.)

For all types of pain

- Glucocorticoids may be beneficial for a variety of types of pain, including neuropathic and bone pain, pain associated with capsular expansion or duct obstruction, pain from bowel obstruction, pain caused by lymphedema, and headache caused by increased intracranial pressure. However, specific recommendations for use of glucocorticoids in the treatment of cancer-related pain are not evidence-based due to limitations in the existing literature. Recommendations are based upon anecdotal experience. (See 'Glucocorticoids' above.)

  In the setting of chronic pain, a typical regimen is dexamethasone 1 to 2 mg twice daily; this may be preceded by a larger loading dose of 10 to 20 mg. A brief period of high-dose glucocorticoids (eg, dexamethasone 50 to 100 mg IV, followed by 12 to 24 mg four times daily, tapered over one to three weeks) is appropriate for "pain crisis" (severe and escalating pain that is not responding sufficiently to an opioid). (See 'Choice of agent and dose' above.)

- For a patient with chronic cancer pain that is poorly responsive to opioid therapy who also has a depressed mood, we suggest an early trial of an analgesic antidepressant (**Grade 2B**). Options include a serotonin-norepinephrine reuptake inhibitor (SNRI) such as duloxetine or a secondary tricyclic drug such as desipramine; bupropion may be considered if cancer pain is complicated by fatigue or somnolence. (See 'Analgesic antidepressants' above.)

- A trial of a transdermal lidocaine patch could be considered in patients who have focal, peripherally-generated pain. Other topical treatments that may be useful in these patients are creams containing a local anesthetic, a NSAID, or capsaicin. (See 'Topical therapies' above.)

- Where available, use of an oromucosal spray containing THC plus cannabidiol (and smaller concentrations of other compounds, nabiximols [Sativex]) may be useful as an adjunctive treatment for refractory pain in patients with advanced cancer. (See 'Cannabis and cannabinoids' above.)

Neuropathic pain — Any of the drugs classified as multipurpose adjuvant analgesics could be considered for a clinical trial in patients with opioid-refractory neuropathic cancer pain. The following reflects our general approach to these patients:

- If neuropathic pain refractory to an opioid is associated with significant depressed mood, we suggest first-line therapy with an antidepressant (**Grade 2B**). Options include a serotonin-norepinephrine reuptake inhibitor (SNRI) such as duloxetine, a secondary tricyclic drug such as desipramine, or possibly bupropion, if the pain is complicated by fatigue or somnolence. (See 'Analgesic antidepressants' above.)

  For patients with neuropathic pain that is not associated with a depressed mood, we suggest first line therapy with gabapentin or pregabalin (**Grade 2C**). We generally prefer pregabalin because of simplified dosing. (See 'Gabapentin and pregabalin' above.)

  Given the positive placebo-controlled trial of duloxetine for painful taxane or platinum-induced neuropathy, duloxetine is an appropriate first-line agent in this setting. However, additional data will be needed to establish the superiority of duloxetine over an alpha-2-delta modulator in these patients, and the efficacy of duloxetine in patients with chemotherapy-induced peripheral neuropathy (CIPN) from other drugs such as vinca alkaloids. (See 'Antidepressants' above and "Prevention and treatment of chemotherapy-induced peripheral neuropathy", section on 'Duloxetine and other antidepressants'.)

- For refractory cases, we suggest second-line therapy with the alternative agent, an antidepressant or an anticonvulsant, depending on which drug was used initially.

- A trial of another anticonvulsant, a cannabinoid (eg, dronabinol), or an alpha-2 adrenergic agonist (eg, tizanidine) could be considered in patients with neuropathic pain that is refractory to opioids and other appropriate adjuvant analgesics. (See 'Alpha-2 adrenergic agonists' above and 'Cannabis and cannabinoids' above and 'Other anticonvulsants' above.)

- A trial of a transdermal lidocaine patch could be considered in patients who have focal, peripherally-generated pain.

Bone pain — Patients with multifocal bone pain are usually managed with a non-steroidal antiinflammatory agent (NSAID), unless they have a specific contraindication to use of these agents, and an opioid, with or without an adjuvant analgesic used specifically for bone pain. (See "Cancer pain management: Use of acetaminophen and nonsteroidal antiinflammatory drugs", section on 'Indications and contraindications'.)

- We recommend the use of bisphosphonates in patients with symptomatic bone metastases from a variety of cancers (**Grade 1A**). Bisphosphonates prevent skeletal-related events; they may also improve pain. (See 'Osteoclast inhibitors' above.)

- Glucocorticoids may be useful in patients with opioid-refractory bone pain, especially in patients with advanced illness or a "pain crisis", which is defined as severe and escalating pain that is not responding sufficiently to an opioid. (See 'Choice of agent and dose' above.)

- The use of bone-targeted radioisotopes is typically reserved for the patient with multifocal bone pain that is refractory to other treatment, whose blood counts are not very low, and who is not expected to require myelosuppressive chemotherapy in the near future. (See 'Bone-targeted radioisotopes' above.)

Bowel obstruction — Medical management of patients with malignant bowel obstruction is focused on control of pain, distention, and vomiting using hydration, opioids, and adjuvant analgesics that may reduce symptoms by lessening peritumoral edema or diminishing intraluminal secretions and peristaltic movements.

- We suggest use of octreotide for the management of GI symptoms in patients with symptomatic inoperable bowel obstruction (**Grade 2B**). (See 'Drugs used for the pain of bowel obstruction' above.)
- In most cases, we use combination therapy rather than octreotide alone. This includes an opioid, an anticholinergic drug such as glycopyrrolate, and a low-dose glucocorticoid such as dexamethasone (1 to 2 mg once or twice daily) (see 'Drugs used for the pain of bowel obstruction' above).

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Topic 2815 Version 45.0

[redacted] [redacted] [redacted] [redacted]

Franklin Medical
GROUP

[redacted]

Chief complaint

- Medical Follow up

History of present illness

[redacted]

Patient here today with past history of Fabry's disease comes in today for followup. We discussed the need for diet as well as exercise. We discussed also discussed the need for general health maintenance as well as vaccines. At this time the patient has a nephrologist in Waterbury. He is now been seen one time and is changed over to Uloric for his gout control as she does have extreme bowel causing severe joint pains. Patient is doing somewhat better. He still could benefit from more pain control this time but is limited due to his end-stage renal disease from his Fabry's disease. At this time strongly recommending and have provided documentation to support his use of marijuana per medical use. At this time as well he still continues to see Dr. [redacted] for depressive type symptoms secondary to chronic pain and chronic medical illnesses and most likely will need to increase his Cymbalta to 90 mg. His breathing remains under fair control on Symbicort. We will continue with Testosterone dosing being ever aware of caution due to coronary disease possibilities

30 minute.

Current medication

- Calcitriol (1,25-dihydroxy D3) 10/02/2014 02:42:00PM Calcitriol 0.25 mcg, 1, Once a Day

Amiodarone Hydrochloride (amiodarone) 200 mg, 3, Once a Day.

Colcrys (colchicine) 0.6 mg, 1, every other day.

Coumadin (warfarin) 2 mg, As Directed.

Cymbalta (duloxetine) 60 mg, 1, Once a Day.

Ensure (GI - Feeding Supplies) -, Once a Day.

Symbicort (budesonide-formoterol) 160 mcg-4.5 mcg/inh, Instructions: INHALE 2 PUFFS EVERY 12 HOURS.

Tylenol with Codeine #3 (acetaminophen-codeine) 300 mg-30 mg, 1, every 4 to 6 hours As Needed.

Uloric (febuxostat) 80 mg, 1, Once a Day.

Allergies

Penicillin.

Review of systems

Gen.: No fever chills or sweats. Positive fatgiue, improved

Skin: No acute skin rashes or skin lesions. Chronic lower extremity edema with erythema noted

Head: No headaches or migraines.

HEENT: No problems chewing or swallowing. No difficulty with hearing.

[redacted] [redacted] [redacted] [redacted]

Neck: No neck pain or stiffness.

Respiratory: Ongoing issues with shortness of breath

Cardiac: BP under fair control, awaiting cardiac ablation

GI: No abdominal pain, nausea, vomiting, diarrhea, or constipation.

Musculoskeletal: Multisystem joint complaints

Neurologic: No issues with syncope, dizziness, or convulsions. Positive neuropathy in loswer extermities from the Fabry's

Psychiatric: depressive symptoms due to chronic medical issues

Metabolic: No issues with diabetes, hypothyroidism, or hyperlipidemia. Positive hypogonadism.

Physical findings

Vital Signs/Measurements	Value	Normal Range	Date
RR	16	12 to 18	10/02/2014 02:37:00PM
PR with BP1	84	50 to 100	10/02/2014 02:37:00PM
Blood pressure (BP1)	154/96	100-120/60-80	10/02/2014 02:37:00PM
Weight	157 lbs	123 to 215	10/02/2014 02:37:00PM
Body mass index	20.7	18 to 25	10/02/2014 02:37:00PM
Height	73 in	65 to 73	10/02/2014 02:37:00PM
Vital Signs:	Value	Normal Range	Date
Temperature	100.1 F		10/02/2014 02:37:00PM
Standard Measurements:	Value	Normal Range	Date
Body surface area	1.92		10/02/2014 02:37:00PM

Gen. health maintenance: Patient has no fever chills or sweats.

Skin examination: No new skin rashes or skin lesions.

Head examination: Normocephalic and atraumatic.

HEENT examination: Eyes are PERRLA, EOMI, nasal mucosa and is moist and pink, oral mucosa is moist and paink.

Pulmonary:Fair air entry bilaterally. Negative wheezes rales or rhonchi

Cardiovascular examination: Heart S1-S2 regular rate and rhythm, negative for murmur, gallops, or abnormal rhythms.

Abdominal examination: Abdomen is soft and nontender with positive bowel sounds. Negative for hepatosplenomegaly. Negative for CVA tenderness.

Extremity examination: Bilateral lower extremity edema to the level of knee. Lower extremity erythema noted as well. Signs of Tophaeous gout

[redacted] [redacted] [redacted] [redacted]

- 10/02/2014 03:14:00PM

Lab Results:

GLYCOHEMOGLOBIN collected on 3/3/2014 8:04:00 AM

Test Name	Result	Abnormal
HEMOGLOBIN A1C	5.7 %	H
HA1C COMMENT HEADING	Certified to the National Glycohemoglobin Standardization Program (NGSP). ADA Guidelines: Increased risk Diabetes Mellitus: A1C 5.7 - 6.4% and fasting blood glucose 100 - 125 mg/dL Diabetes Mellitus: A1C >6.5% and fasting blood glucose >125 mg/dL	

PROLACTIN collected on 3/3/2014 8:04:00 AM

Test Name	Result	Abnormal
PROLACTIN	17.73 ng/mL	H
PROLACTIN REFERENCE RANGE HEADING	****Reference Ranges**** Male: 2.64 - 13.13 ng/mL Female: Premenopausal: 3.34 - 26.72 ng/mL Postmenopausal: 2.74 - 19.64 ng/mL	

FOLLIICLE STIMULATING HORMONE,S collected on 3/3/2014 8:04:00 AM

Test Name	Result	Abnormal
FSH REF RANGE HEADING	****Reference Ranges**** Male: 1.3 - 19.3 mIU/mL Female: Follicular Phase: 3.9 - 8.8 mIU/mL Mid Cycle Peak: 4.5 - 22.5 mIU/mL Luteal Phase: 1.8 - 5.1 mIU/mL Post Menopausal: 16.7 - 113.6 mIU/mL	
FSH	6.7 mIU/mL	

LUTEINIZING HORMONE,SERUM collected on 3/3/2014 8:04:00 AM

Test Name	Result	Abnormal
LUTEINIZING HORMONE	4.3 mIU/m	
	**** Reference Ranges**** Male: 1.2 - 8.6 mIU/mL Female:	

[redacted] [redacted] [redacted] [redacted]

LH REFERENCE RANGE HEADING	Follicular Phase: 2.1 - 10.9 mIU/mL Mid Cycle Peak: 19.2 - 103.0 mIU/mL Luteal Phase: 1.2 - 12.9 mIU/mL Post Menopausal: 10.9 - 58.6 mIU/mL

TESTOSTERONE, T.BIO,FREE,S collected on 3/3/2014 8:04:00 AM

Test Name	Result	Abnormal
Testosterone, Bioavailable, S	29 ng/dL	L
Testosterone, Free, S	6.9 ng/dL	L
Testosterone, Total, S	300 ng/dL	

Tests

Follow-up PRN (FU PRN).

Assessment

#1. Fabry's disease: Continue working with nephrology at this point. Patient is currently going to be entering a renal transplant list. Due to the severity of his end-stage renal disease all nonsteroidal anti-inflammatories cannot be used at this time. Patient has failed Gabapentin, Lyrica, as well as narcotics causing no pain relief for his neuropathy secondary to his Fabry's disease. There is plenty of literature to support the use of marijuana in neuropathy especially polyneuropathy, Which I have attached.

#2. Depression: Continue working with Dr. [redacted] at this time. We'll consider increasing his Cymbalta to 90 mg on his next visit

#3. Atrial fibrillation: Continue with his current medications as well as continue with Coumadin

#4. Gout: Slowly improving on Uloric, still with severe joint pains.

#5. Hypogonadism: Continue with monthly Testosterone injections.

Vaccinations

08/30/2005 PCV.

Visit narration updated 10/2/2014 3:15:33 PM by [redacted]

Electronically Signed by: [redacted] MD 10/2/2014 3:15:00 PM

UCONN HEALTH
263 Farmington Avenue
Farmington, CT 06030
Phone: 860-679-2000

PATIENT PLAN

[redacted]

09/16/2014 10:00 AM
Visit Type: Office Visit

Thank you for choosing us for your healthcare needs. The following is a summary of the outcome of today's visit and other instructions and information we hope you find helpful.

Reason(s) for visit: Follow Up of Kidney disease.

Assessment/Plan

#	Detail Type	Description
1.	Assessment	Chronic kidney disease, stage V (585.5), chronic, Symptomatic.
	Plan Orders	Today's instructions / counseling include(s) contact Dr [redacted] office, continue current medications, labs pre-infusion Friday 9/19, no NSAIDs, no salt diet and start calcitriol daily. He is to schedule a follow-up visit 6 Months.
2.	Assessment	GOUT NOS (274.9), chronic, Improved.
	Plan Orders	Today's instructions / counseling include(s) continue meds per Dr [redacted].
3.	Assessment	ANEMIA IN CHR KIDNEY DIS (285.21).
	Plan Orders	Today's instructions / counseling include(s) increase iron to twice daily as tolerated.
4.	Assessment	Lipidosis (272.7), chronic.
	Plan Orders	Albumin, Serum, BUN, CBC W/ Diff $, CHOL, Total$, CL, CO2, Creatinine, GFR, HDL CHOL$, Ionized Calcium,Serum $, K, LDL CHOL$, Magnesium, Serum (MG) $, NA, Phosphorus, Serum, Trig$ and Uric Acid, Serum to be performed. Today's instructions / counseling include(s) will arrange for measurement of GL3 in next few weeks.

Medications Active Post Today's Visit:

Brand Name	Dose	Sig Description	Comments
DICYCLOMINE HCL	10 mg	take 1 capsule by oral route 3 times every day	pt. states compliant
SYMBICORT	80 mcg-4.5 mcg/actuation	inhale 2 puff by inhalation route 2 times every day in the morning and evening	
WARFARIN SODIUM	2 mg	takes as directed	pt. states compliant
FUROSEMIDE	40 mg	take 1 tablet (40MG) by oral route 2 times every day	pt. states compliant
AMIODARONE HCL	200 mg	take 1 tablet by oral route every day	pt. states compliant
ALLOPURINOL	100 mg	take 2 Tablet by oral route every day	

LIDODERM	5 % (700 mg/patch)	apply 1 patch by transdermal route every day (May wear up to 12hours.)
FABRAZYME	35 mg	infuse (1MG/KG) by intravenous route every 2 weeks
COLCRYS	0.6 mg	take 1 tablet by oral route every 2 days
MEDROL	4 mg	take as directed
CALCITRIOL	0.25 mcg	take 1 capsule by oral route every day

Allergies:

Ingredient	Reaction	Medication Name	Comment
PENICILLINS			

BP/Temp/Pulse/Respiration

BP (mm/Hg)	Temp F	Temp C	Pulse/min	Resp/min
138/82			60	

Height/Weight/BMI

Height Ft	In	cm	Weight lb	oz	kg	BMI (kg/m2)
6	0	182.88	155		70.307	21.02

Instructions/Education:

Order
continue current medications
no salt diet
no NSAIDs
continue meds per Dr [redacted]
increase iron to twice daily as tolerated.
will arrange for measurement of GL3 in next few weeks
labs pre-infusion Friday 9/19
start calcitriol daily
contact Dr [redacted] office

Orders this encounter:

Order	Provider	Status	Reason	Side	Interpretation	Result
Urinalysis, automated w/scope	[redacted] MD	result received			see detail	Color: yellow. Glucose: negative. Bilirubin: negative. Ketones: negative. Specific Gravity: 1.015. Blood: trace-lysed. pH: 5.5. Albumin: 100. Urobilinogen: 0.2. Nitrite: negative. Leukocytes:

			negative.
follow-up visit 6 Months	[redacted] MD	ordered	
LDL CHOL$	[redacted] MD	ordered	
Trig$	[redacted] MD	ordered	
CO2	[redacted] MD	ordered	
Creatinine	[redacted] MD	ordered	
GFR	[redacted] MD	ordered	
Ionized Calcium,Serum $	[redacted] MD	ordered	
K	[redacted] MD	ordered	
Albumin, Serum	[redacted] MD	ordered	
BUN	[redacted] MD	ordered	
CBC W/ Diff $	[redacted] MD	ordered	
CL	[redacted] MD	ordered	
Magnesium, Serum (MG) $	[redacted] MD	ordered	
NA	[redacted] MD	ordered	
Phosphorus, Serum	[redacted] MD	ordered	
Uric Acid, Serum	[redacted] MD	ordered	
CHOL, Total$	[redacted] MD	ordered	
HDL CHOL$	[redacted] MD	ordered	
Referrals: Nephrology. [redacted] MD. Assume care	[redacted] MD	ordered	close to dialysis

Referrals

Status	Physician	Timeframe	Appointment
ordered	Referrals: Nephrology. [redacted] MD. Assume care	2 Weeks	

Follow-up:

Assessment	Follow-up	Reason	Timeframe	Comments
585.5	follow-up visit 6 Months		6 Months	

The patient was checked out at 11:24 AM by [redacted].

Sincerely,

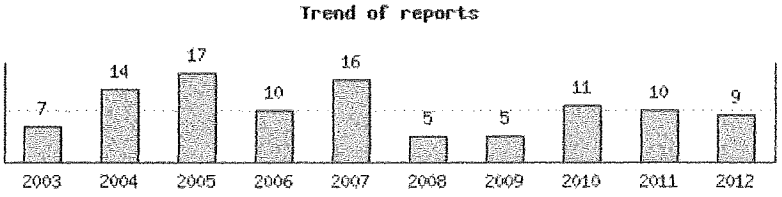
Provider: [redacted] MD 09/16/2014 11:25 AM

Nephrology - CM3
UConn Health – Dept Of Nephrology
263 Farmington Ave Cm Suite 3
Farmington, CT 060303835

From FDA reports: drug interactions between Fabrazyme, Enalapril Maleate for a Male patient aged 38

This is a personalized study for a 38 year old male patient. The study is created by eHealthMe based on reports of 104 people who take the same drugs and have drug interactionsfrom FDA.

On Aug, 5, 2014: **104** people who reported to have interactions when taking Fabrazyme, Enalapril Maleate are studied



Information of the patient in this study:

Age: 38

Gender: male

Conditions: Fabry's Disease

Drugs taking:
- Fabrazyme
- Enalapril Maleate
- Fabrazyme
- Enalapril Maleate

Drug interactions have: Pain In Extremity, Rigors

eHealthMe real world results:

Comparison with this patient's adverse outcomes among males aged 38 (±5):

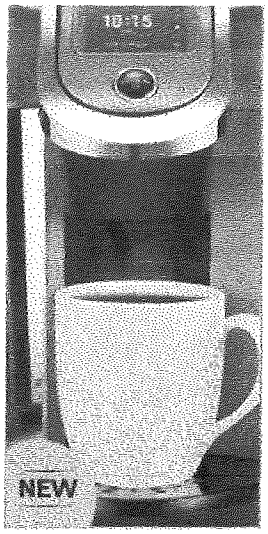
Interaction	Number of reports
Pain In Extremity	4 (50.00%)
Rigors (an episode of shaking or exaggerated shivering)	7 (87.50%)

Most common interactions experienced by males aged 38 (±5) in the use of Fabrazyme, Enalapril Maleate:

Interaction	Number of reports
Chills (felling of cold)	8
Rigors (an episode of shaking or exaggerated shivering)	7
Atrial Fibrillation (fibrillation of the muscles of the atria of the heart)	6
Weight Increased	4
Pain In Extremity	4
Cholelithiasis (the presence or formation of gallstones in the gallbladder or bile ducts)	3
Flushing (the warm, red condition of human skin)	3
Hernia (hernia happens when part of an internal organ or tissue bulges through a weak area of muscle)	2
Umbilical Hernia (an outward bulging (protrusion) of the abdominal lining or part of the abdominal organ(s) through the area around the belly button)	2
Gallbladder Disorder	2

Most common interactions experienced by males aged 38 (±5) in long term use of Fabrazyme, Enalapril Maleate:

None.



Related studies

- Enalapril Maleate side effects
- Fabrazyme side effects

Related conditions

- Pain in extremity

Related drug side effects

- Pain In Extremity
- Rigors

For people in general (regardless of gender or age):

Comparison with this patient's adverse outcomes:

Interaction	Number of reports
Pain In Extremity	20 (19.23%)
Rigors (an episode of shaking or exaggerated shivering)	13 (12.50%)

Most common interactions experienced by people in the use of Fabrazyme, Enalapril Maleate:

Interaction	Number of reports
Cardiac Failure Congestive	38
Condition Aggravated (worse condition)	32
Atrial Fibrillation (fibrillation of the muscles of the atria of the heart)	24
Mitral Valve Incompetence (inefficient heart valve)	22
Chills (felling of cold)	21
Ventricular Extrasystoles (premature cardiac contraction)	20
Pain In Extremity	20

Infusion Related Reaction	18
Cardiac Failure	16
Tricuspid Valve Incompetence (inefficient heart valve)	16

Most common interactions experienced by people in long term use of Fabrazyme, Enalapril Maleate:

Interaction	Number of reports
Cardiac Failure Congestive	15
Blood Pressure Increased	10
Stridor	9
Somnolence (a state of near-sleep, a strong desire for sleep)	9
Syncope (loss of consciousness with an inability to maintain postural tone)	9
Tricuspid Valve Incompetence (inefficient heart valve)	8
Mitral Valve Incompetence (inefficient heart valve)	8
Pneumonia	8
Renal Failure Acute (rapid kidney dysfunction)	6
Condition Aggravated (worse condition)	6

How to use the study: print a copy of the study and bring it to your health teams to ensure drug risks and benefits are fully discussed and understood.

You can also:

- **Subscribe the study**: get notified of updates
- **Post a comment**: or see what other people said about the study
- **Join a mobile peer support group:**
  - group for people who take Fabrazyme and have Pain In Extremity
  - group for people who take Enalapril Maleate and have Pain In Extremity
  - group for people who take Fabrazyme and have Rigors
  - group for people who take Enalapril Maleate and have Rigors

Recent user comments

- "in addition to the big white bumps i also am getting ... " (3 minutes ago)

- "I am very concerned about the weight gain. I have gai ... " (2 hours ago)

- "I am now off of diltiazem due to the horrible side ef ... " (2 hours ago)

Recent mobile support groups

- Polycythemia Vera
- Polycythemia Rubra Vera
- Primary Polycythemia
- Alcohol and Polycythemia Vera
- Erectile Dysfunction and Flonase

Medical cannabis can improve appetite, ease chronic pain, say researchers

Published on January 25, 2013 at 5:14 AM · No Comments

Though controversial, medical *cannabis* has been gaining ground as a valid therapy, offering relief to suffers of diseases such as cancer, Post-Traumatic Stress Disorder, ALS and more. The substance is known to soothe severe pain, increase the appetite, and ease insomnia where other common medications fail.

In 2009, Zach Klein, a graduate of Tel Aviv University's Department of Film and Television Studies, directed the documentary Prescribed Grass. Through the process, he developed an interest in the scientific research behind medical marijuana, and now, as a specialist in policy-making surrounding medical *cannabis* and an MA student at TAU's Porter School of Environmental Studies, he is conducting his own research into the benefits of medical *cannabis*.

Using marijuana from a farm called Tikkun Olam - a reference to the Jewish concept of healing the world - Klein and his fellow researchers tested the impact of the treatment on 19 residents of the Hadarim nursing home in Israel. The results, Klein says, have been outstanding. Not only did participants experience dramatic physical results, including healthy weight gain and the reduction of pain and tremors, but Hadarim staff saw an immediate improvement in the participants' moods and communication skills. The use of chronic medications was also significantly reduced, he reports.

Klein's research team includes Dr. Dror Avisar of TAU's Hydrochemistry Laboratory at the Department of Geography and Human Environment; Prof. Naama Friedmann and Rakefet Kelder of TAU's Jaime and Joan Constantiner School of Education; Dr. Yehuda Baruch of TAU's Sackler Faculty of Medicine and director of the Abarbanel Mental Health Center; and Dr. Moshe Geltzen and Inbal Sikorin of Hadarim.

Cutting down on chronic medications

Israel is a world leader in medical *cannabis* research, Klein says. The active ingredient in marijuana, THC, was first discovered there by Profs. Raphael Mechoulam and Yechiel Gaoni. Prof. Mechoulam is also credited for having defined the endocannabinoid system, which mimics the effects of *cannabis* and plays a role in appetite, pain sensation, mood and memory.

In the Hadarim nursing home, 19 patients between the ages of 69 and 101 were treated with medical *cannabis* in the form of powder, oil, vapour or smoke three times daily over the course of a year for conditions such as pain, lack of appetite, and muscle spasms and tremors. Researchers and nursing home staff monitored participants for signs of improvement, as well as improvement in overall life quality, such as mood and ease in completing daily living activities.

During the study, 17 patients achieved a healthy weight, gaining or losing pounds as needed. Muscle spasms, stiffness, tremors and pain reduced significantly. Almost all patients reported an increase in sleeping hours and a decrease in nightmares and PTSD-related flashbacks.

There was a notable decline in the amount of prescribed medications taken by patients, such as antipsychotics, Parkinson's treatment,

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mood stabilizers, and pain relievers, Klein found, noting that these drugs have severe side effects. By the end of the study, 72 percent of participants were able to reduce their drug intake by an average of 1.7 medications a day.

Connecting cannabis and swallowing

This year, Klein is beginning a new study at Israel's Reuth Medical Center with Drs. Jean-Jacques Vatine and Aviah Gvion, in which he hopes to establish a connection between medical *cannabis* and improved swallowing. One of the biggest concerns with chronically ill patients is food intake, says Klein. Dysphagia, or difficulty in swallowing, can lead to a decline in nutrition and even death. He believes that *cannabis*, which has been found to stimulate regions of the brain associated with swallowing reflexes, will have a positive impact.

Overall, Klein believes that the healing powers of *cannabis* are close to miraculous, and has long supported an overhaul in governmental policy surrounding the drug. Since his film was released in 2009, the number of permits for medical *cannabis* in Israel has increased from 400 to 11,000. His research is about improving the quality of life, he concludes, especially for those who have no other hope.

Source:
American Friends of Tel Aviv University

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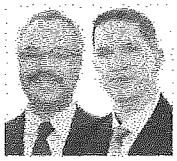
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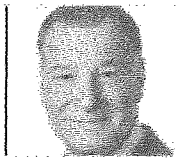
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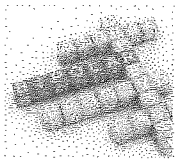
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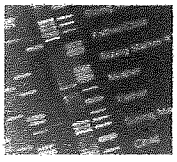
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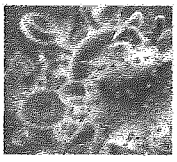
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