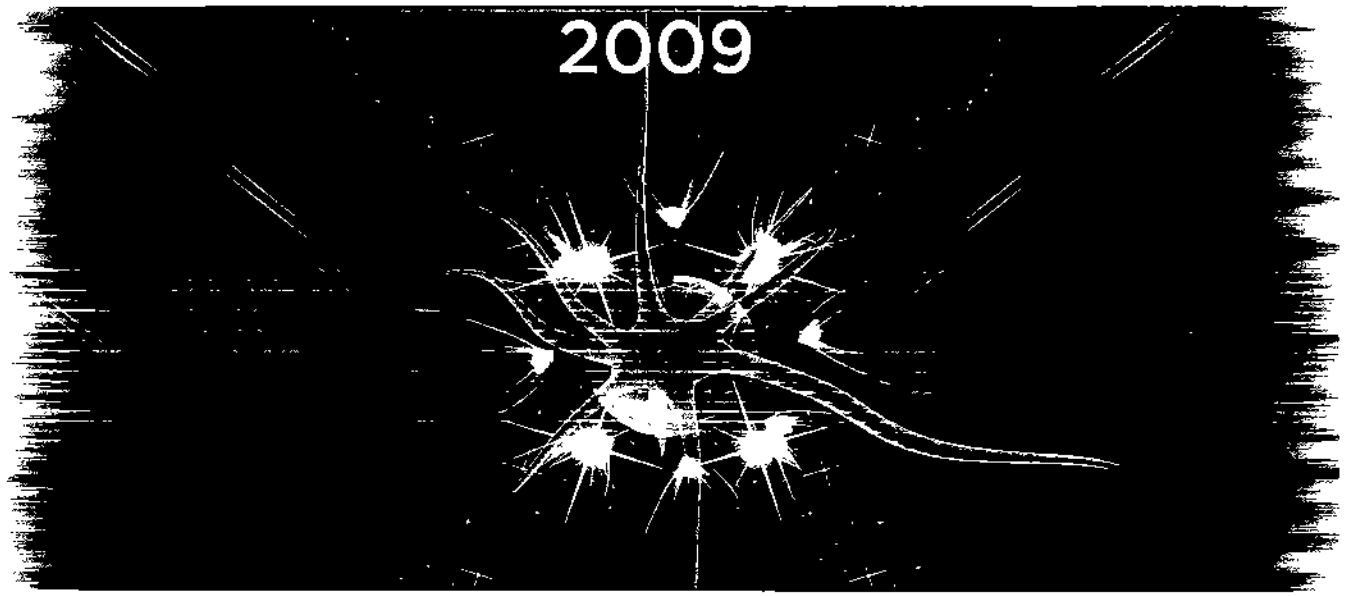
Current Treatments in the Management of Diabetic Peripheral Neuropathic Pain 2009



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DISCLOSURES

Dr. Argoff consults for and is on the speakers' bureaus of Eli Lilly, Endo Pharmaceuticals and Pfizer.
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Dr. Samraj has no relevant financial relationships to disclose.

Diabetes remains the most common cause of non-traumatic limb loss in the United States, with diabetic peripheral neuropathy (DPN) the most prominent culpable factor.[1] Of the 42,500 nontraumatic amputations in the United States in 2004, neuropathy was considered the major contributing factor in 87%.[2]

Unfortunately, DPN is widely underdiagnosed. A 2005 survey by the American Diabetes Association (ADA) (N=8,119) indicated that for most of the respondents who experienced symptoms of DPN (75%), the condition had not been diagnosed.[3] Furthermore, most of the symptomatic respondents (56%) were unfamiliar with the term *diabetic neuropathy*.

In a 2007 Position Statement, the ADA recommended that all patients with diabetes be screened at least annually for DPN.[4] Recent data indicate that the positive predictive value of the 128-Hz tuning fork is better than those of more complex neuropathy scoring systems and monofilament testing for efficiently diagnosing DPN[5]; hence, diagnosing DPN should be well within the ability of every primary care clinician.

The prevalence of DPN is compelling: Neuropathy will develop in 25% to 50% of patients with diabetes in their lifetime.[6] A recent prospective study followed 1,172 patients with type 1 diabetes, none of whom had neuropathy at baseline. After 7.3 years of follow-up, 23.5% of the patients had neuropathy.[7]

Table 1. Conditions To Consider In Differential Diagnosis of DPN

Amyloid neuropathy, paraproteinemia

Autoimmune disorders
Lupus, Behçet's syndrome, Sjögren's syndrome, antiphospholipid antibody syndrome

Chemotherapy, including platinum-based therapy

Demyelinating polyneuropathies
Guillain-Barré syndrome

Endocrine abnormalities
Hypothyroidism, acromegaly

Hereditary neuropathies
Hereditary sensory and autonomic neuropathy, Charcot-Marie-Tooth disease, Friedreich's ataxia

HIV medications: nucleoside analogs
Zalcitabine, stavudine, didanosine

Infections
Hepatitis B and C, HIV, Lyme disease, leprosy

Inflammatory nerve disorders
Vasculitis, chronic inflammatory demyelinating polyradiculopathy, sarcoidosis, primary biliary cirrhosis

Malignancies
Neoplasms, lymphoma, Hodgkin's lymphoma, multiple myeloma, paraneoplastic syndromes

Medications
Amiodarone, colchicine, isoniazid, hydralazine, metronidazole, nitrofurantoin, phenytoin, lipid-lowering agents (statins, fibrates)

Nutraceuticals
Supratherapeutic pyridoxine use

Nutritional deficiency in vitamins B_1 and B_{12}, folate, or copper

Prolonged exposure to cold or hypoxia

Renal disorder

Toxic exposure to alcohol, arsenic, lead, mercury, or organophosphorus compounds

DPN, diabetic peripheral neuropathy
Based on references 14-16.

Table 2. Suggested Screening Laboratory Panel

Antinuclear antibodies, rheumatoid factor

Complete blood cell count

Comprehensive metabolic panel, lipid profile

C-reactive protein or erythrocyte sedimentation rate

HIV, hepatitis B and C

Serum and urine protein electrophoresis

Serum and urine protein immunofixation electrophoresis

Thyroid function

Urinalysis

Vitamin B_{12}, methylmalonic acid, homocysteine, folate, vitamin B_1, vitamin B_6

Based on references 18-20.

The most common presentation of DPN is diabetic peripheral neuropathic pain (DPNP), which typically manifests as burning, shooting, or stabbing pain in the feet or lower legs.[8,9] Rarely, similar symptoms in the arms/hand can occur but are almost always preceded by leg symptoms.

DPNP is highly problematic for patients for several reasons. First, the pain is often worse at night, depriving patients of sleep and thereby causing fatigue. Also, DPNP has a strong negative effect on numerous quality-of-life (QoL) indicators and activities of daily living, especially because the pain is often worsened by activity.[10,11] Finally, the treatments available before 2004 were often limited by adverse-event profiles, providing a suboptimal risk–benefit ratio, and none was approved by the FDA for the treatment of DPNP.[12]

The cause of DPNP remains unknown, but several theories have been suggested. Neuropathy is included among the microvascular complications of diabetes, reflecting the philosophy that DPNP is a consequence of microvascular damage to the vasa nervorum. Studies have suggested that impaired nitric oxide synthesis plays an important role in the pathogenesis of DPNP.[9]

Differential Diagnosis

Patients suspected of having neuropathy should undergo a comprehensive history and physical (including neurologic) assessment because the causes of neuropathy in patients with diabetes can range from simple benign processes to malignancy (Table 1).[13-15] Although it is tempting to automatically consider typical neuropathies in patients with diabetes as DPN, several clinical trials have indicated that other disorders often masquerade as or contribute to symptoms indistinguishable from those of DPN. Indeed, in one trial 55% of patients with a diagnosis of DPN ultimately were found to have additional etiologic or contributory factors.[16]

The initial step in the evaluation of DPN is to establish the presence of neuropathy. DPN manifests as neuropathic symptoms distributed symmetrically in a stocking–glove pattern. Once a diagnosis of neuropathy has been made, laboratory screening (Table 2) to rule out other contributing or etiologic factors is appropriate.[16-19]

A provisional diagnosis of DPN may be made when patients present with either positive neuropathic symptoms (tingling, burning, or prickling sensations, sharp pains, and touch hypersensitivity) or negative neuropathic symptoms (numbness, insensitivity, loss of proprioceptive sense, loss of balance) in the absence of other potential etiologies.[20,21]

Treatment Goals

The goals of treatment include the following:

Pain modulation. The term *modulation* is preferred to *remission* in recognition of the fact that even with adequate treatment, few patients will experience complete resolution of pain symptoms.

In our discussion of pharmacotherapies, we commonly refer to at least 2 currently recognized measures of pain relief: a 30% reduction in pain from baseline and a 50% reduction in pain from baseline, both of which are validated indicators. Studies have shown that regardless of the baseline pain score, a 30% reduction in pain is a "meaningful" reduction to patients.[22,23] Patients with a reduction in pain of 50% often describe themselves as "mostly better." Although we may not always be capable of completely abolishing pain, reductions of 30% to 50% are important markers of clinical efficacy. Clinicians should be wary of claims that describe "statistically significant pain relief" unless that reduction in pain is also a "clinically significant" reduction in pain.

Pain scales are useful for assessing pain intensity and response to treatment. Although a 10-point pain scale is functional for patients with DPNP in whom nocturnal pain may be particularly problematic, a pain scale that allows diurnal pain mapping may be more useful. Furthermore, patients may be better able to communicate their pain symptoms if given such descriptors to use as "nuisance," distracting," "disabling," and "worst possible." Clinicians may add further detail by asking patients to map out when their least, worst, and average pain occurs (Figure 1), so that they can specifically target treatment regimens to problematic time periods. Figure 2 modifies the scale to reflect a common presenting scenario for the typical DPNP patient.

Patient education. It is incumbent on clinicians to provide patients with information on the symptoms of DPN and the risks associated with this condition. It is the opinion of the authors that the educational component of diabetes care typically provided by diabetes educators should be offered on an annual basis or more often, as patient needs indicate.

Restoration of function. Although pain control is a key goal of treatment, improvement in function is also of great importance to the patient. Patients may require referral to a physical/occupational therapist to enhance function.

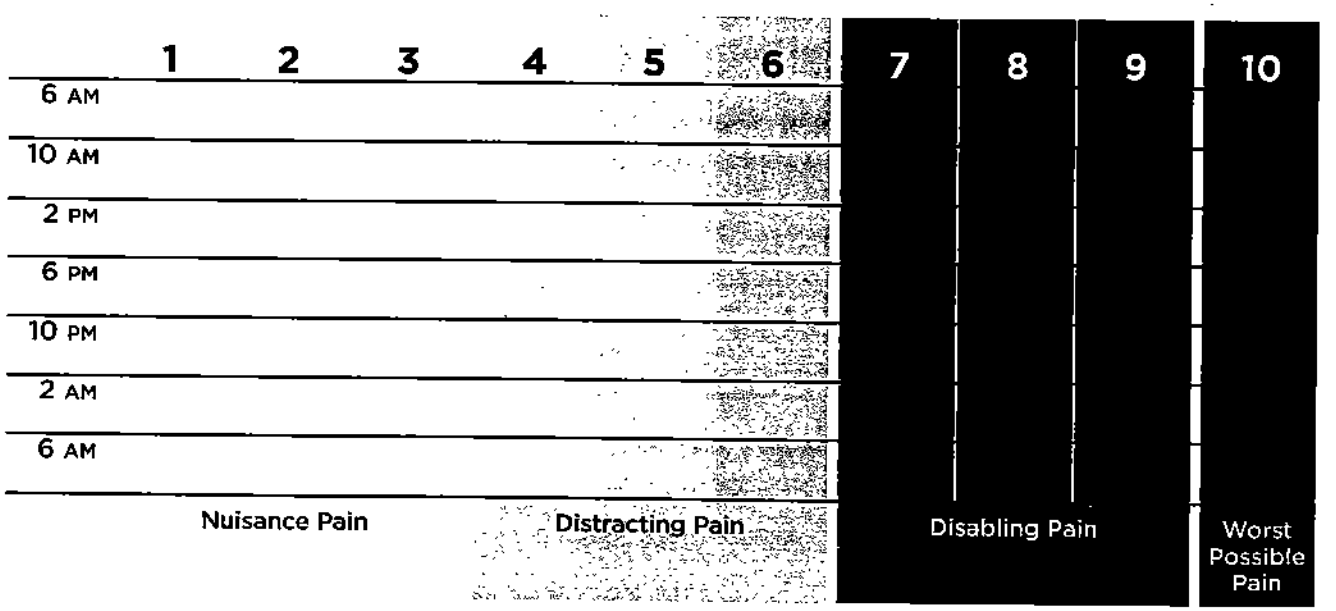

Figure 1. An adaptation of the traditional 10-cm visual analog scale.

Patients are asked to think about the levels of pain that they experience throughout the day and mark when the pain occurs (on the vertical scale) and how intense their pain is (on the horizontal scale), noting when it is least (L), average (A), and worst (W).

Nuisance pain (eg, postexercise muscle soreness, postvaccination soreness)

Distracting pain (eg, menstrual cramps [day 3], osteoarthritis pain at rest)

Disabling pain (eg, migraine, persistent toothache)

Worst possible pain (eg, labor, kidney stone)

Adapted from Kuritzky L, Weaver A. Advances in rheumatology: coxibs and beyond. *J Pain Symptom Manage*. 2003;25(suppl 2):S6-S20.

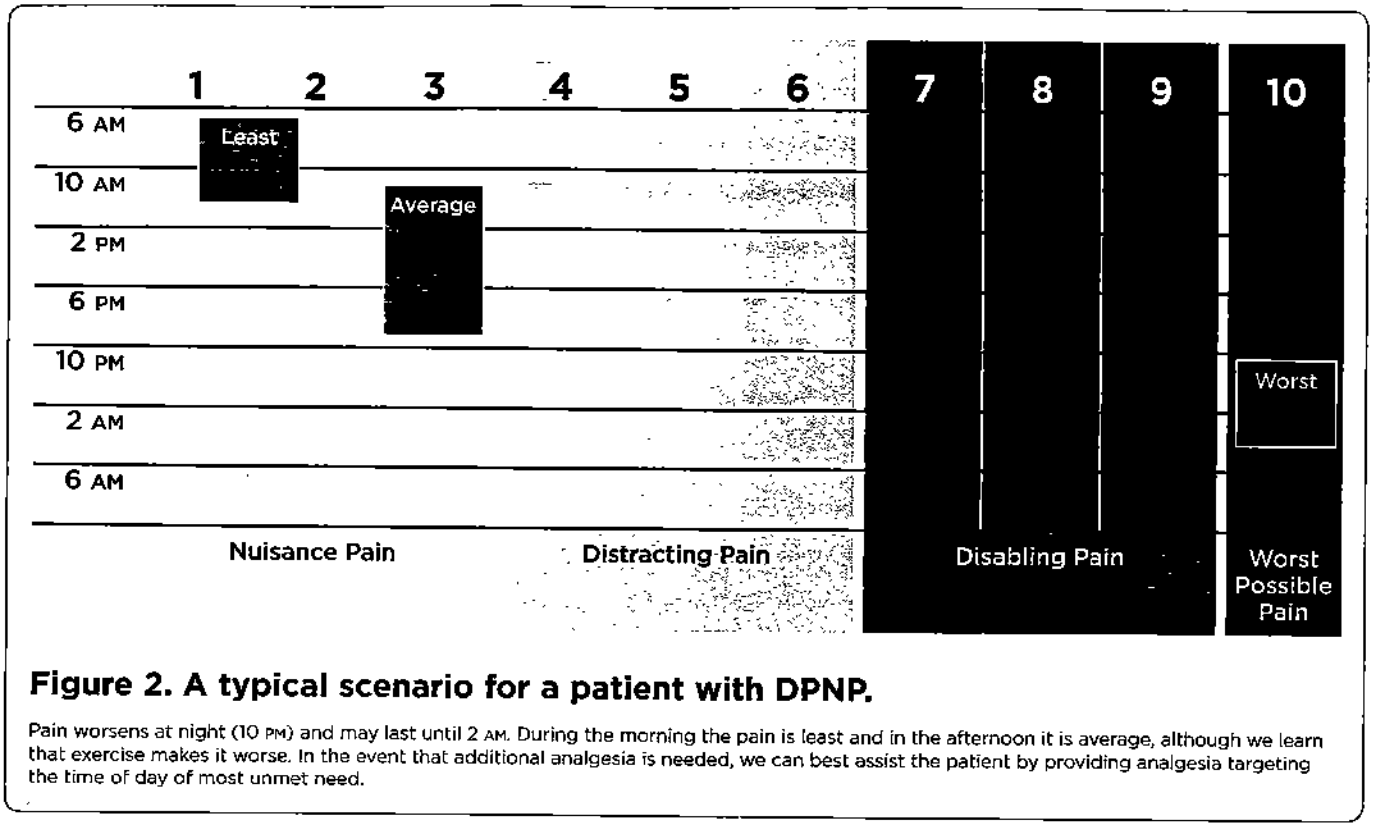

Figure 2. A typical scenario for a patient with DPNP.

Pain worsens at night (10 PM) and may last until 2 AM. During the morning the pain is least and in the afternoon it is average, although we learn that exercise makes it worse. In the event that additional analgesia is needed, we can best assist the patient by providing analgesia targeting the time of day of most unmet need.

Enhanced diabetic control. Both the United Kingdom Prospective Diabetes Study and the Diabetes Control Complications Trial (DCCT) demonstrated a curvilinear relationship between hemoglobin A_{1c} (Hb A_{1c}) levels and microvascular end points, documenting the value of tight control of glucose.[24,25] Recently, an extension of the DCCT showed that the reduction in risk for neuropathy conferred by tight glucose control persisted during 8 years of follow-up.[26]

FDA-Approved Treatments

Currently, duloxetine (Cymbalta, Lilly) and pregabalin (Lyrica, Pfizer) are the only medications that have been approved by the FDA for the treatment of DPNP (Table 3).[27,28] These 2 agents as well as others that are commonly used off-label for the treatment of DPNP are described below.

Duloxetine

Duloxetine is indicated for the management of neuropathic pain associated with DPN; depression; and fibromyalgia. The drug is marketed under the same trade name (Cymbalta) used when it is indicated for the treatment of depression. In trials of duloxetine for DPNP, patients with underlying depression were specifically excluded; hence, the beneficial effects of duloxetine on DPNP should not be mistakenly attributed to its effects on depression.

Duloxetine provides balanced norepinephrine and serotonin reuptake inhibition; it is to this pharmacologic effect that its therapeutic impact on pain is attributed. Investigators have suggested that an endogenous pain-dampening system is mediated through a dual norepinephrine–serotonin response in the central nervous system. Clinical experience has corroborated that some agents that simultaneously modify both norepinephrine and serotonin may favorably affect pain syndromes, in contrast to selective serotonin reuptake inhibitors, which have little efficacy.[29]

Clinical pharmacology. Because of its long plasma half-life (approximately 12 hours), duloxetine can be dosed once per day.[30] This agent is highly protein-bound and may increase the plasma levels of other highly protein-bound drugs when administered simultaneously. The primary routes of metabolism of duloxetine are through the cytochrome P-450 (CYP) isoenzymes CYP2D6 and CYP1A2. Inhibitors of CYP1A2 (eg, fluvoxamine, quinolones) may increase the area under the curve of duloxetine.[18] Additionally, concomitant use of duloxetine with potent inhibitors of CYP2D6 increases the concentration of duloxetine.[30] Finally, duloxetine is a moderate 2D6 inhibitor; hence, clinicians should be vigilant for interactions with drugs metabolized by the 2D6 P-450 pathway.

Clinical trial data. In a 12-week multicenter, double-blind, placebo-controlled trial, the currently approved dosage (60 mg once per day) was studied in patients with long-standing diabetes (mean, 11.4 years) and DPNP for at least 6 months (mean, 3.7 years).[31] Most of the patients had type 2 diabetes (88%), were male (61%), and were white (77%).

At baseline, the patients' mean 24-hour average pain score was approximately 6 on an 11-point scale (0-10), indicating moderate to severe pain. Within 1 week, a

statistically significant reduction in the 24-hour average pain score was found in the 60-mg duloxetine group compared with the placebo group. By week 2, the clinically meaningful 30% reduction threshold was achieved, and this improvement was maintained throughout the 12-week study. By the end of the trial, 49% of the 60-mg duloxetine group had achieved a reduction in pain of at least 50%.

A second short-term study looked specifically at nighttime pain.[32] Within 1 week, a statistically significant reduction in the mean level of nighttime pain was found, and by week 2, a 30% reduction was achieved. By study end (12 weeks), 40% to 50% of the patients receiving duloxetine experienced a reduction in nighttime pain of at least 50%. Long-term open-label studies do not show any diminution of analgesic efficacy.[33]

In addition, data from a 12-week trial linked duloxetine (both 60 and 120 mg/d) with reductions in pain that interfered with patient functioning, as measured by the Brief Pain Inventory–Interference portion.[34] By the end of the trial, patients experienced a more than 50% reduction in pain that interfered with 7 domains of functioning: general activity, mood, walking ability, normal work, relationships with others, sleep, and enjoyment of life.

A pooled analysis of 3 placebo-controlled trials demonstrated that variables such as duration of diabetes, degree of glycemic control, and insulin treatment do not undermine the efficacy of duloxetine in patients with DPNP.[35]

Adverse-event profile. The most common adverse event associated with duloxetine in clinical trials is nausea.[27] In the trial by Goldstein et al, nausea was experienced by 16.7% of patients in the duloxetine group (vs 9.6% of patients in the placebo group).[31] Fortunately, most patients who experience nausea related to duloxetine perceive it as mild to moderate. Additionally, nausea appears to be a transient phenomenon, usually occurring within the first week of treatment and then dissipating.

Weight loss. In placebo-controlled clinical trials of duloxetine treatment for DPNP, patients treated with duloxetine for up to 13 weeks showed a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.[27]

Glycemic control. Some concerns exist regarding potential changes to glucose levels. In an analysis of 3 clinical trials (N=1,024), treatment with duloxetine resulted in slight changes to patients' glycemia.[36]

Safety profile. For all medications used to treat depression, such as duloxetine, recent FDA mandates insist that specific language detailing an increased risk for suicidal ideation be included. This is the case whether or not depression is the intended target of treatment. No deaths or suicide attempts have been reported among people studied in the clinical trials of duloxetine for DPNP.

Serious adverse hepatic events have been reported rarely among patients on duloxetine; because of comorbidities that could independently have caused these events, the causal relationship between duloxetine and serious hepatic events remains indeterminate. Ultimately, duloxetine is not recommended for persons with active liver disease.[27]

Duloxetine should not be used in combination with a monoamine oxidase inhibitor (MAOI) or within at least 14 days after discontinuation of treatment with an MAOI.[27]

Clinical use. The authors recommend initiating duloxetine treatment at a dose of 20 to 30 mg per day for 1 week to allow acclimatization and to obviate nausea, although there are no clinical trials to support this methodology. In the trial by Goldstein et al, which included a 20-mg dose of duloxetine as part of a dose-ranging segment of the study, the incidence of nausea with the 20-mg dose was not significantly different from that with placebo.[31]

For patients who experience moderate relief while using 60 mg per day and who tolerate this dose well, it is appropriate to consider a dose of 120 mg per day to determine whether a further improvement in pain control will occur. However, it should be noted that a dose of 120 mg per day is associated with a higher incidence of adverse events than is a dose of 60 mg per day. It is unlikely that patients who do not achieve meaningful results after a 6-week course of the 60-mg dose will respond to increased dosing. Nonresponders should be switched to a different medication.

No trials have been conducted of duloxetine in combination with any other pharmacotherapy other than acetaminophen. It is up to the clinician to decide whether combinations of any off-label agents with or without duloxetine are appropriate. Duloxetine is not a controlled substance and is not known to have abuse potential.

It is recommended that the duloxetine capsule not be opened and mixed with food or beverage for administration. The capsule contains small, enteric-coated pellets, which are acid-labile. Once the duloxetine capsule has negotiated the acid environs of the stomach, it effectively dissolves in the more alkaline pH of the small intestine. Removing the pellets from the capsule compromises their ability to withstand the effects of stomach acid, potentially defeating the opportunity for absorption. For similar reasons, the capsule should not be crushed or dissolved.

Pregabalin

Pregabalin is indicated for the management of neuropathic pain associated with DPN, postherpetic neuralgia, and fibromyalgia. It is also indicated to treat partial-onset seizures in adults who are already taking at least one other antiseizure medicine.

Clinical pharmacology. The pharmacologic effects of pregabalin are thought to be mediated through activity at the $\alpha_2\delta$ subunit of presynaptic calcium channels in the central nervous system.[37,38] Its mechanism of action appears to be similar to that of gabapentin in that both agents bind to the $\alpha_2\delta$ subunit. Pregabalin does not

Table 3. General Overview of Duloxetine and Pregabalin

	Duloxetine	Pregabalin
Mechanism of action	Selective serotonin and norepinephrine reuptake inhibitor	Binds to calcium channel $\alpha_2\delta$ ligand
FDA-approved indications	Neuropathic pain associated with DPN, major depressive disorder, fibromyalgia	Postherpetic neuralgia, DPN, fibromyalgia, adjunctive therapy for adults with partial-onset seizures
Controlled substance class	Not a controlled substance	Schedule V (abuse potential is low)
How supplied	Capsules: 20, 30, and 60 mg	Capsules: 25, 50, 75, 100, 150, 200, 225, and 300 mg
Dosage for DPNP	60 mg/d without regard to meals; may be increased up to 120 mg/d The authors recommend an initial dosage of 20 to 30 mg/d for 1 wk to allow acclimatization and reduce the incidence/severity of nausea	Starting dose: 50 mg tid Maximum dose: 100 mg tid after 1 wk; dose should be adjusted for patients with renal impairment
Effective (30%) pain reduction within	2 wk	1 wk
Oral bioavailability	Absorbed at alkaline pH (>5.5); gastroparesis, elevated gastric pH may alter absorption (theoretical)	Well absorbed; steady therapeutic levels after 24-48 h
Solubility	Bound (>90%) to proteins	Not bound to proteins
Effect of food	Can be taken with or without food	Can be taken with or without food
Metabolism	Hepatic CYP2D6 and CYP1A2	Renal
Elimination	Renal: approximately 70% excreted in urine as metabolites of drug; approximately 20% excreted in feces	Renal: approximately 90% excreted in urine as unchanged drug
Half-life	12 h	6 h
Patients with renal impairment	*Mild to moderate renal insufficiency:* consider lower starting dose and titrate *Severe renal impairment:* not recommended	CrCl 60 mL/min: no dose adjustment CrCl 30-60 mL/min: 150 mg/d CrCl 15-30 mL/min: 75 mg/d CrCl <15 mL/min: 25-50 mg/d Hemodialysis: consult package insert for supplementary dose schedule
Hepatic effect	Not recommended for patients with substantial alcohol use or chronic liver disease	No effect
Routine monitoring	None required	None required
Gender	No effect	No effect
Ethnicity	Not studied	Effect does not vary with ethnicity
Geriatric population	No significant change	No significant change in patients with normal CrCl
Pregnancy category	C[a]	C[a]
Lactation	Effect in humans unknown (not recommended)	Effect in humans unknown (not recommended)
Overdose	No antidote; supportive therapy should be given Activated charcoal may be useful in limiting absorption	No antidote Hemodialysis may be indicated (50% reduction in 4 h)

[a] No adequate and well-controlled studies have been performed in pregnant women. The drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

CrCl, creatinine clearance; **CYP,** cytochrome P-450; **DPN,** diabetic peripheral neuropathy; **DPNP,** diabetic peripheral neuropathic pain
Based on references 27 and 28.

interact with the CYP enzyme system. It has the capacity to mildly affect the PR interval, so caution is appropriate in patients who have a prolonged PR interval or who may be receiving other agents that can prolong the PR interval.

Because pregabalin is renally excreted, dose adjustment is appropriate for patients with impaired renal function (Table 3).

Clinical trial data. In an 8-week placebo-controlled trial of 100 mg of pregabalin 3 times daily in patients with diabetes (N=146) and long-standing DPNP (mean duration, 9.4 years), Rosenstock et al found significant improvements (>30% reduction in pain) in the pregabalin group by week 1.[39] Patients entered the trial with a mean pain score of 6 on an 11-point Likert scale. The majority of patients had type 2 diabetes, were white, and were male.

Pain control was maintained throughout the trial. A 50% reduction in the mean pain score was achieved by 40% of the pregabalin group versus 14.5% of the placebo group. Improvements in sleep occurred during week 1 and were maintained throughout the study. Other QoL measures (eg, Short Form-36 Bodily Pain subscale score) also improved.[24]

Another randomized controlled trial of pregabalin for DPNP used doses as high as 600 mg per day.[40] The patient demographics were similar to those in other trials, but this trial lasted only 5 weeks. In the segment of the trial comparing 300 mg of pregabalin per day (n=81) with placebo (n=97), reductions in pain of at least 30% were found within 1 week, and a substantial number of patients (46%) achieved and maintained at least a 50% reduction in pain from baseline. As in the Rosenstock study, improvements in sleep were found within 1 week.

The maximum recommended dose of pregabalin in the treatment of DPNP is 300 mg per day. Doses of pregabalin of 150 mg per day are unlikely to provide benefit for patients with DPNP unless they have renal insufficiency. In a 6-week randomized, placebo-controlled, double-blind multicenter trial of 246 patients with DPNP, pregabalin at 150 mg per day provided no advantage compared with placebo.[41] The study also showed that dosing at 600 mg per day was as effective as dosing at 300 mg per day but was linked to a greater frequency of adverse events.

Adverse-event profile. The rate of withdrawal from pregabalin clinical trials because of adverse events is low, approximately 11%, and the dropout rate is associated with higher doses.[39,42]

The most commonly reported adverse event is mild to moderate dizziness, occurring in as many as 27% to 39% of subjects at 300 mg per day.[42] Also common are somnolence (23.5% of patients taking 300 mg) and peripheral edema (7%-10.5%).[39,40] Most adverse events (85%) were described as mild to moderate. Women and older subjects reported adverse events more often than did men and younger patients.[39]

Peripheral edema may be problematic with pregabalin, especially during coadministration with thiazolidinediones. In clinical trials, peripheral edema was found in 8% (69 of 859) of patients taking pregabalin alone and in 19% (23 of 120) of those taking it with a thiazolidinedione. Caution is advised for patients with heart failure because of the potential for weight gain and edema when pregabalin and thiazolidinediones are coadministered.[42]

Weight gain. Weight gain, not necessarily related to edema, may occur during the administration of pregabalin. In clinical trials, 8% of diabetic patients treated with pregabalin versus 2% of placebo recipients gained 7% of their baseline weight during 13 weeks of treatment. In a cohort of 333 patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg, but no effect on HbA_{1c} was noted. Weight gain does not appear to be related to baseline body mass index, sex, or race.[14]

Weight gain in patients with diabetes is somewhat more problematic when pregabalin is coadministered with a thiazolidinedione; it was noted in 7.5% (9 of 120) of patients on both drugs versus 4% (35 of 859) of those on pregabalin alone.

Safety profile. Like all antiepileptic agents, pregabalin should be withdrawn gradually (over a minimum of 1 week) to reduce the potential for increased seizure frequency in patients with seizure disorders.[29]

In clinical trials, no serious adverse events or deaths were attributable to pregabalin.

Clinical use. Pregabalin has a rapid onset of action, with clinically relevant reduction in pain achieved within the first week of use. The recommended initial dose is 50 mg 3 times daily, which can be titrated to a full therapeutic dose of 100 mg 3 times daily within one week if the medication is well tolerated.[28] The authors suggest that patients be started on 50 mg twice daily. Because somnolence and dizziness may be limiting for some patients, it may be helpful to administer the initial doses at night to minimize the consequences of these adverse effects.

Pregabalin is a controlled substance (Schedule V, abuse potential low). This status was suggested subsequent to the observation that in controlled trials (N=5,500), a small percentage of individuals (4%) reported euphoria (vs 1% taking placebo).[28] In selected study populations, a somewhat greater incidence of euphoria (up to 12%) has been seen.[28] Similarly, symptoms suggesting pregabalin dependency (eg, insomnia, nausea, headache, or diarrhea) have occasionally occurred upon discontinuation of treatment.[14] In addition, a small trial (N=15) involving recreational substance users showed that participants rated pregabalin as providing a "high" comparable to that achieved with 30 mg of oral diazepam. Schedule V is the lowest-risk classification status and includes such agents as diphenoxylate. Certain low-dose codeine preparations (eg, Robitussin AC, Wyeth) also have a Schedule V classification.

Pregabalin has not been studied in combination with, or in comparison with, any other pharmacologic entity. It is up to the clinician to decide whether

any combinations of off-label agents with or without pregabalin are appropriate.

Non–FDA-Approved Agents

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) such as amitriptyline have been the mainstay of neuropathic pain treatment for more than 3 decades. Because most patients with DPNP are at midlife or older, potential cardiovascular toxicity, as well as other α-adrenergic, histaminergic, and anticholinergic adverse effects, must be considered before TCAs are prescribed. Nonetheless, because a large number of clinical trials confirm their efficacy in various neuropathic pain syndromes[22] and because they are generally inexpensive and fairly well tolerated at the low doses typically used for neuropathic pain, TCAs may be considered a first-line therapy.

Gabapentin

Gabapentin has shown favorable results in the treatment of DPNP in doses ranging from 300 to 1,200 mg 3 times daily. In a trial involving 165 patients with DPNP, patients randomized to gabapentin showed a significant reduction in mean pain scores within 2 weeks.[43] This effect was maintained during the 8-week study. In addition, the gabapentin group showed significantly greater improvement in QoL and sleep interference scores.

α-Lipoic Acid

In contrast to the treatments previously described, which relieve symptoms related to DPN/DPNP, α-lipoic acid (ALA) is the only intervention currently documented to mitigate (reverse) the neuropathy itself.[44] Although published clinical trials have shown conflicting findings, overall results with ALA appear favorable both for improvements in nerve function and reduction of symptoms.

In the SYDNEY 2 trial, treatment with oral ALA at 600 mg per day for 5 weeks resulted in a reduction of 50% or higher in total symptom score in 62% of patients.[45] Significant improvements were also found in neuropathy symptoms and change score, neuropathy impairment score, and patients' global assessment of efficacy.

Topical Lidocaine

The lidocaine patch 5% (Lidoderm, Endo) has shown great promise as a treatment for DPNP. An open-label trial was carried out with 56 patients, who received up to 4 lidocaine patches 5% for up to 18 hours per day.[46] Prescribing information for this agent recommends the simultaneous use of up to 3 patches for up to 12 hours per day within a 24-hour period. However, data from this open-label study suggest that use of 4 patches for up to 18 hours per day is well tolerated.[46]

In this 3-week trial, patients achieved a statistically significant reduction in pain by the end of the study.[46] Interestingly, patients with allodynia did not respond as well as those without allodynia. Nonetheless, by week 3, both subgroups showed a clinically relevant and statistically significant 30% reduction in pain from baseline.

Venlafaxine

The serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine extended-release (Effexor XR, Wyeth) has shown efficacy in the treatment of DPNP, but generally at higher doses. In a placebo-controlled trial involving 244 patients with DPNP, only venlafaxine extended-release at doses of 150 to 225 mg per day provided both statistically significant and clinically relevant pain reduction.[47]

Because higher doses of venlafaxine are associated with increases in pulse rate and blood pressure,[48] the latter of which is particularly consequential in patients with diabetes, this agent should be reserved for those for whom an SNRI is preferred when duloxetine is not tolerated or available.

Opioids

Opioid treatment has sometimes been described as ineffective for neuropathic pain. However, recent data have suggested that for neuropathic pain, higher doses of opioids may be required to attain satisfactory pain reduction. Since 1998, 5 double-blind, randomized controlled trials have shown a statistically significant reduction in pain and improvements in sleep among patients taking opioids.[23]

A small placebo-controlled trial showed that high-dose oxycodone controlled-release (80 mg/d) provided a statistically significant and clinically meaningful reduction in DPNP.[49] However, the adverse-event profile of oxycodone was problematic. In addition, the withdrawal of a large percentage of both the oxycodone and placebo groups from the study (43% and 50%, respectively) hampers the interpretation of these results.

Tramadol

Tramadol is often grouped with opioids because it does have a weak μ-receptor activity; however, it also modulates serotonin and norepinephrine. Two trials have shown significant pain relief with tramadol doses of up to 400 mg per day.[22] The most common adverse events were dizziness, nausea, constipation, and somnolence.[50] In addition, seizures have been reported with use of tramadol in the recommended dose range.[50]

The authors recommend that tramadol dosing begin at 50 to 100 mg per day, titrated by 50 to 100 mg every 3 to 7 days. Dosing should not exceed 400 mg per day.[50] Tramadol is also available in an extended-release formulation.

Topical Nitrates

Because DPNP is considered a microvascular disorder with endothelial dysfunction, it has been theorized that local application of nitroglycerin or isosorbide

dinitrate—which are nitric oxide donors—may remedy some of the pathophysiologic defects attending to DPNP. In a small placebo-controlled, randomized, crossover trial (N=22), patients with DPNP were advised to apply a single spray of isosorbide dinitrate to both feet before bedtime.[51] The spray produced a statistically significant and clinically meaningful reduction (>30%) in pain score by the end of the trial. Although the product used in this trial is not available in the United States, nitroglycerin spray is available.

Capsaicin

Although some data suggest that capsaicin has efficacy in the management of DPNP, it has numerous stark limitations. First, the initial application of capsaicin itself induces burning. Second, it takes days to weeks for capsaicin to achieve sufficient depletion of substance P to reduce pain. Third, it must be applied multiple times per day (at least 3 times daily, and preferably 4 times daily) to maintain analgesic efficacy. Finally, if therapy is interrupted for more than 24 hours, repletion of substance P again requires sustained application of capsaicin, with attendant initial burning, to once more accomplish depletion. Although these obstacles are not insurmountable, and some individuals may actually prefer such a topical treatment, these inconveniences diminish the potential for widespread use.

Conclusion

Because of the substantial effect of DPNP on numerous aspects of QoL, timely diagnosis and treatment are essential. The initial choice of therapy is likely to be based on clinician, patient, or caregiver

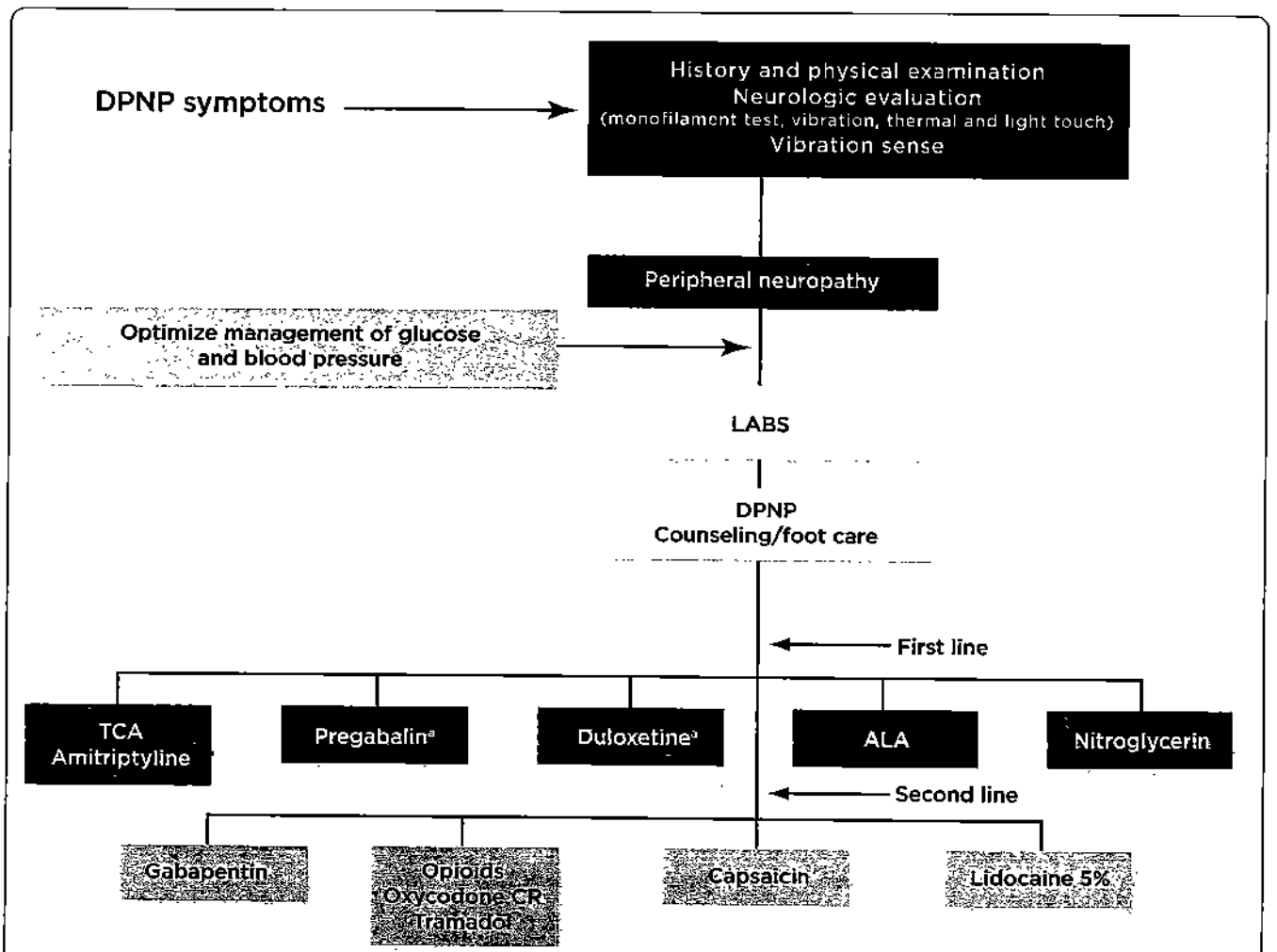

Figure 3. An approach to the management of DPNP.

[a] FDA-approved for DPNP.
ALA, α-lipoic acid; **CR,** controlled-release; **DPNP,** diabetic peripheral neuropathic pain; **LABS,** laboratory screening; **TCA,** tricyclic antidepressant

preferences regarding frequency of dose administration, adverse-event profile, mechanism of action, cost, and potential for drug interactions.

A suggested algorithm for the treatment of DPNP is shown in Figure 3. The authors recommend that patients be informed of the various choices available and allowed to participate in a patient-centered, negotiated decision of therapy. Patients often require multiple pharmacotherapies to achieve pain control; hence, clinicians should not be discouraged when monotherapy does not achieve full symptom remission. As in the management of diabetes itself, when one medication has provided partial control, it is generally accepted that the next therapy should be added to, rather than substituted for, the initial therapy. However, some clinicians may wish to explore the full therapeutic potential of more than one monotherapy before expanding the treatment regimen to multiple drugs.

Because no direct head-to-head trials have compared any of these individual agents with another (except TCAs), conclusive proof of the superiority of one agent over another is lacking. On the other hand, any of the agents listed in the algorithm may be tried and the metric of the currently recognized 30% reduction from baseline pain used as an indication of success, alone or in combination with other agents, despite the lack of FDA indication for combination therapy. Clinicians should be confident that the vast majority of persons with DPNP can be successfully managed with one or more of the pharmacotherapeutic tools available.

Neurologic Considerations in Diabetic Peripheral Neuropathy

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Drs. Kuritzky and Samraj have discussed effectively many key aspects regarding the current assessment and treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN). As a neurologist and pain specialist, I would like to offer additional insights regarding this condition.

Although the exact mechanisms of DPN are unknown, several key hypotheses have emerged.

Oxidative stress may result in the production of free radicals and, subsequently, potential neural ischemia, and impairment of normal neural metabolism and axonal transport.[1] Abnormalities in the **polyol pathway** due to hyperglycemia result in accumulation of sorbitol and fructose, which in turn leads to decreased neural myoinositol, disturbed axonal transport, abnormal membrane Na+/K+-ATPase activity and other changes that can disrupt normal action potential propagation.[2] **Nonenzymatic glycosylation,** also known as **glycation** (the reaction of hyperglycemia with lipids, proteins and nucleotides), may result in disruption of normal axonal transport and neural metabolism as a consequence of altered neuronal integrity and normal repair mechanisms.[3,4]

Although the authors describe key clinical features of neuropathic pain associated with DPN, they do not distinguish among the different types of diabetic neuropathy. Peripheral neuropathy associated with diabetes may present with a variety of sensory, motor and autonomic symptoms. In addition to the distal symmetric type of DPN—the type that is most commonly studied and characterized—other types of diabetic neuropathy deserve mention.

A subtype of the distal symmetric polyneuropathy is one that involves mostly small-diameter sensory fibers. In this form, deep tendon reflexes may remain normally active as the patient complains mostly of burning, aching and crushing pain concurrent with the loss of pain and temperature sensation. Symptoms tend to be worse at night. Autonomic disturbance

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may be part of a more generalized diabetic neuropathy and, in rare cases, can be the sole manifestation of diabetic neuropathy in a patient. Abnormal pupil response to light, dysfunction of bowel and bladder, cardiac arrhythmia, sweating abnormalities and orthostatic hypotension are among the signs of autonomic neuropathy.

The asymmetric neuropathies should not be overlooked. These include carpal tunnel syndrome (median neuropathy within the wrist), cervical radiculoplexopathy, thoracic radiculopathy, lumbosacral radiculoplexopathy and various cranial mononeuropathies. In patients with diabetes, localized (focal) neuropathies, such as carpal tunnel syndrome, may be caused by entrapment and compression of the affected nerve, with subsequent ischemia and infarction of the affected nerve. Asymmetric neuropathies, which occur as a consequence of nerve infarction, may involve a single nerve (mononeuropathy) or multiple nerves (mononeuritis multiplex). These neuropathies often present acutely with severe pain. Diabetic thoracic radiculoneuropathy is associated with severe burning, stabbing pain, is often unilateral in onset and may be associated with significant hyperesthesia and allodynia over the affected area. It affects patients over the age of 50 and needs to be distinguished from zoster sine herpete (acute herpes zoster—shingles—which occurs without a rash). Eventually, bilateral symptoms may occur. Apoplectic onset of unilateral pain either in the hip/lower back or shoulder/neck may occur in diabetic patients with diabetic lumbosacral radiculoplexopathy or cervical radiculoplexopathy. Weakness usually develops within days or weeks of the pain and bilateral involvement may ultimately occur. Most patients will improve over months; however, some patients will experience residual neurologic deficits.

Specific clinical trials for treatment of the pain associated with these less common forms of DPN are lacking; thus, the clinician must consider the available evidence for the more common form of painful diabetic neuropathy when choosing an analgesic regimen for patients with the painful asymmetric forms—being fully aware that the data may not be directly extrapolated.[5,6]

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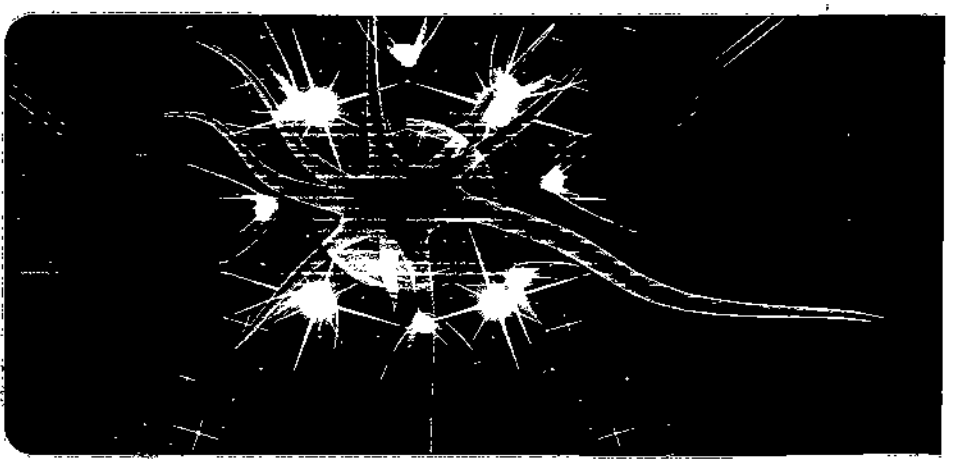

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