Curr Diab Rep (2013) 13:500–508
DOI 10.1007/s11892-013-0396-6

New and Developing Drugs for the Treatment of Neuropathic Pain in Diabetes

Roy Freeman

Published online: 15 June 2013
© Springer Science+Business Media New York 2013

Abstract A number of agents from diverse pharmacological classes are used to treat neuropathic pain associated with diabetic peripheral neuropathy. Only three of these have regulatory approval for this indication in the U.S. In this focused article, I will discuss selected drugs, newly approved or in development, to treat neuropathic pain in patients with diabetic neuropathy. These will include agonists and antagonists of the transient receptor potential channels, a family of receptor proteins that play a role in the transduction of physical stress; sodium channel isoform specific antagonists; a recently approved dual-action opioid receptor agonist–norepinephrine reuptake inhibitor; gene therapy for neuropathic pain; and anti-nerve growth factor molecules. Mechanisms of action, preclinical supporting data, clinical trial evidence, and adverse effects will be reviewed.

Keywords Neuropathic pain · Diabetic peripheral neuropathy · TRPV1 · TRPA1capsaicin · Sodium channel antagonists · NaV1.7 · Anti-NGF antibodies · Gene therapy · Tapentadol · Diabetes

Introduction

A variety of agents from diverse pharmacological classes are used to treat neuropathic pain associated with diabetic peripheral neuropathy. Several of these have the approval of regulatory authorities, while the use of others is based on data from randomized clinical trials and/or inferences about mechanism of action. At present, only seven agents are approved for the treatment of neuropathic pain in the U.S. These are lidocaine (5 %) administered via a transdermal patch, gabapentin, duloxetine, pregabalin, gabapentin administered in a gastro-retentive form, capsaicin (8 %) administered via a transdermal patch, and tapentadol.

It is notable that of these seven agents, only three—pregabalin, duloxetine, and tapentadol—have regulatory approval in the U.S. for the treatment of painful diabetic peripheral neuropathy. This is despite the large prevalence of diabetes, diabetic peripheral neuropathy, and neuropathic pain associated with diabetic peripheral neuropathy. Epidemiologic studies estimate the worldwide prevalence of diabetes as 366 million persons in 2011 and 566 million persons in 2030 (*International Diabetes Federation Global Atlas of Diabetes*, 5th ed.; http://www.idf.org/diabetesatlas/5e/the-global-burden). Neuropathic pain is present in up to 25 % of individuals with diabetes [1–4].

In this focused article, I will discuss selected drugs newly approved or in development to treat neuropathic pain in diabetic neuropathy. This is not an exhaustive review. I will adopt a molecular-target-based approach [5], while recognizing that most drugs have more than one molecular target. Only oral and topical agents will be covered. Intravenous and intrathecal agents will not be covered in this article.

Transient Receptor Potential Channels

Background

The transient receptor potential (TRP) channels are a family of receptor proteins that play a role in the transduction of physical stress. Several of these channels (TRP vanilloid type 1–4 [V1-4], TRP melastin type 8 [M8], and TRP ankyrin type 1 [A1]) play a role in nociception.

TRPV1 is expressed in small- and medium-diameter nociceptor sensory neurons, although recent reports have

R. Freeman (✉)
Center for Autonomic and Peripheral Nerve Disorders,
Beth Israel Deaconess Medical Center, One Deaconess Road,
Boston, MA 02215, USA
e-mail: rfreeman@bidmc.harvard.edu

suggested a more widespread distribution [6, 7]. Activation of the TRPV1 receptor leads to the opening of the nonselective cation channel, allowing the influx of sodium and calcium ions and the consequent depolarization of nociceptor afferent neurons. The role of the TRPV1 receptor in neuropathic pain is not fully elucidated. There is conflicting evidence as to whether TRPV1is upregulated in neuropathic pain models and in humans with neuropathic pain [8, 9].

TRPV1 Agonists: Topical

The vanilloid capsaicin, the pungent component in hot chili peppers, is widely used as a topical agent to treat neuropathic and musculoskeletal pain [10]. The mechanisms whereby topical capsaicin leads to pain relief are unknown. Physiological desensitization of the nociceptor neurons follows the initial activation; however, with repeated application, degeneration of nociceptor [11–13] and autonomic [14] nerves occurs. The mechanism of capsaicin-induced neurodegeneration is not fully elucidated. TRPV1-mediated calcium influx [15] with subsequent glutamate release is most likely implicated [16, 17]. The desensitization and subsequent degeneration may underlie the analgesic effects of capsaicin.

Topical application of capsaicin as a repeatedly applied low-concentration cream (0.075 %) has been used therapeutically to provide pain relief in several neuropathic pain conditions [10, 18]. There is evidence derived from randomized clinical trials that application of low-concentration capsaicin (0.025 %–0.075 %), 4 to 5 times daily for up to 8 weeks, is effective in treating patients with neuropathic pain due to diabetic neuropathy [19–21] (although not in all studies) [22] and other neuropathic pain conditions [23–25]. Several weeks of therapy may be required to attain a therapeutic benefit. This has prompted the development and use of capsaicin in higher concentrations.

Successful studies of a single application of 8 % capsaicin applied as a patch to the painful site for 30–90 min have led to the approval in the U.S. of this high-concentration patch for the treatment of postherpetic neuralgia [26•, 27, 28]. While in Europe, regulatory authorities have approved the 8 % capsaicin patch for the treatment of peripheral neuropathic pain in nondiabetic adults (either alone or in combination with other medicinal products for pain).

Studies evaluating the treatment of neuropathic pain due to HIV neuropathy using this patch are conflicting. In one study, pain improved following 30- and 90-min but not 60-min applications) [29]. The U.S. Food and Drug Administraton's (FDA) Anesthetic and Analgesic Drug Products Advisory Committee's review of two pivotal clinical trials of the 8 % capsaicin patch did not find "substantial evidence" of effectiveness.

Studies are currently in progress to investigate the efficacy and safety of 8 % capsaicin in painful diabetic peripheral neuropathy. In the 12-week, phase III efficacy study, the single application of capsaicin (8 %) is compared with placebo in reducing pain intensity in individuals with painful diabetic peripheral neuropathy (http://clinicaltrials.gov/ct2/show/NCT01533428). In a 64-week long-term study, the safety of capsaicin (8 %) applied repeatedly to the feet for 30 or 60 min is assessed in individuals with pain caused by nerve damage in diabetic patients (http://clinicaltrials.gov/show/NCT01478607).

There are theoretical concerns about capsaicin application to regions subject to pressure in individuals with preexisting nerve damage. Capsaicin applied in low [11, 13, 14] and 8 % [30] concentration results in substantial small-fiber sensory and autonomic denervation. There is also associated impaired neurogenic inflammation with loss of nociceptor, sudomotor, and pilomotor axon reflexes [14, 31]. Due to distal peripheral nerve degeneration, these protective responses are often impaired at baseline in diabetic and other small-fiber neuropathies [32–35]. This impairment plays a central role in the predisposition of diabetic patients to foot ulceration and amputation [36, 37]; a peripheral neuropathy in individuals with diabetes leads to a 7-fold increase in the risk of foot ulceration [38, 39]. Long-term outcome studies specifically addressing this question are necessary. The primary outcome measure in the long-term safety study is the percentage change in health-related quality of life (http://clinicaltrials.gov/show/NCT01478607).

TRP Antagonists: Oral

The efficacy and safety of small-molecule TRPV1 antagonists in the treatment of pain have been investigated in phase I and phase II clinical trials. These trials have been complicated by serious adverse events, including hyperthermia and clinically significant impairment in noxious heat perception. In one study, impaired heat perception was sufficient to result in oral burns of mild to moderate intensity (http://www.astrazenecaclinicaltrials.com/_mshost800325/content/clinical-trials/resources/pdf/D5090C00019; http://www.astrazenecaclinicaltrials.com/search/?itemId=8595834). It remains unclear as to whether these adverse effects are universal in this class of agents or whether new molecular entities may avoid these therapeutically limiting adverse events.

Antagonists to other TRP channels involved in nociception, including TRPV3, TRPV4, TRPM8, and TRPA1, are in the planning stage or early development. TRPA1, a cation channel that functions as a cellular sensor that detects mechanical, chemical, and thermal stimuli, is of interest. The channel is largely expressed in primary sensory neurons that mediate somatosensory processes and nociceptive transmission. Preclinical evidence from animal models shows that TRPA1 plays a role in neuropathic and

inflammatory pain [40•, 41, 42]. Additional clinical support for the role of this channel in pain modulation comes from the report of an association between a gain of function mutation of the gene encoding TRPA1 and an autosomal-dominant familial episodic pain syndrome characterized by episodes of debilitating upper body pain, triggered by fasting and physical stress [43]. Currently, phase 1 and 2 clinical trials for acute pain, chronic pain, and diabetic peripheral neuropathic pain (http://clinicaltrials.gov/ct2/show/NCT01726413) are in the planning stages.

Sodium Channels

Background

Voltage gated sodium channels are membrane proteins that mediate the generation and transmission of electric currents in excitable cells [44]. Nine sodium channel isoforms exist [Na(v)1.1–Na(v)1.9], each having unique biophysical properties and nervous system distribution [45]. Na(v)1.7, Na(v)1.8, and Na(v)1.9 are expressed in peripheral sensory neurons, and Na(v)1.3 is upregulated along pain-signaling pathways after nerve injury [44, 46–49].

Several lines of evidence support a role for sodium channels in neuropathic pain. These include the following: (1) Changes in sodium channel expression after nerve injury [e.g., Na(v)1.3 expression is increased in rodent nerve injury models, and Na(v)1.3 and Na(v)1.6 are upregulated in a rodent model of diabetes) [44, 46–49]; (2) increased sodium channel expression and lidocaine-sensitive spontaneous discharges occur at the site of nerve injury [50, 51]; (3) gain-of-function missense mutations in *SCN9A*, the gene that encodes for Na(v)1.7, have been shown to cause the inherited pain disorders, primary erythermalgia, and paroxysmal extreme pain disorder [52•, 53]; (4) loss of function nonsense mutations in *SCN9A* leads to channelopathy-associated insensitivity to pain, a disorder in which affected individuals are unable to perceive physical pain [54–56]; and (5) single amino-acid substitutions in *SCN9A* found in 30 % of a cohort of idiopathic SFN patients produce gain-of-function changes in sodium channel Na(v)1.7 [57••, 58]. These data not only support a potential role for sodium channel antagonists in the treatment of neuropathic pain, but further provide the rationale for the use of sodium channel isoform specific antagonists. The more specific approach to sodium channel antagonism may improve the narrow therapeutic window; dose-related adverse events are frequently the limiting factor when the nonspecific sodium channel antagonists currently available are used.

Sodium Channel Isoform Antagonists

Several Na(v) 1.7 antagonists are in varying stages of development. Phase II studies investigating the efficacy and safety of these agents in different conditions are in progress or have been completed. Disorders under study include primary, inherited erythromelalgia (http://www.clinicaltrials.gov/ct2/show/NCT01769274), postherpetic neuralgia using a topically applied Na(v) 1.7 antagonist (http://www.clinicaltrials.gov/ct2/show/NCT01195636), chronic neuropathic low back pain (a negative trial; http://clinicaltrials.gov/show/NCT01019824), lumbosacral radiculopathy (http://www.clinicaltrials.gov/ct2/show/NCT01561027), and trigeminal neuralgia (http://www.clinicaltrials.gov/ct2/show/NCT01540630).

Diabetic neuropathic pain trials are in the planning stage. Preclinical data showing increased expression of Na(v) 1.7 in some [59, 60], although not all, studies [47], allied with the reports of Na(v) 1.7 variants that produce gain-of-function changes in channel properties in idiopathic small-fiber neuropathy, lend support to this approach to therapy in painful diabetic peripheral neuropathy [57••, 58]. Antagonists to other specific sodium channels that may be implicated in peripheral neuropathic pain Na(v) 1.3, Na(v) 1.6, and Na(v) 1.8 are at earlier stages of development.

Enthusiasm for this approach to sodium channel antagonism should be tempered by the observation that neuropathic pain persists in mutant mice null for Na(v)1.3, Na(v)1.7, and Na(v)1.8 [61, 62].

Opioid Receptor Agonism: Norepinephrine Reuptake Inhibition

Background

Four opioid receptors exist: the μ (mu) opioid receptor, the δ (delta) opioid receptor, the κ (kappa) opioid receptor, and the opioid like receptor 1 (ORL1). These receptors are activated by exogenous and endogenous opioid ligands and are found throughout the central and peripheral nervous system, on endocrine cells, and on immune cells. Activation of the mu receptor most consistently produces analgesia [63, 64]. Several randomized controlled trials have shown that opioids can effectively treat neuropathic pain due to diabetic peripheral neuropathy, postherpetic neuralgia, phantom limb, and other causes [65–70].

A descending pain-modulating circuit, with origins in cortical and subcortical regions, projects to the spinal cord via the midbrain and plays an important role in modulating the pain experience. The monoamines—norepinephrine acting on spinal alpha-adrenoreceptors, serotonin acting on serotonin (5-HT) receptors, and dopamine acting on

dopaminergic (D) receptors in the spinal cord—are the major neurotransmitters of these pathways. Activation of these receptors may be facilitatory or inhibitory, depending on the receptor subtype and site of activation [71]. The monoamine reuptake inhibitors increase synaptic monoamine levels and directly influence the activity of these descending neurons. The opioids also interact with these pathways [63, 64].

Tapentadol

Tapentadol is a novel, centrally acting analgesic that exerts its analgesic effects through both μ-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition (NRI). The dual MOR–NRI mechanism has been elucidated in preclinical studies that demonstrated reversal of analgesia in neuropathic pain models by both the MOR antagonist, naloxone, and alpha-2-adrenorecptor antagonists, yohimbine and atipamazole [72, 73]. There are minimal serotonergic effects. The parallel noradrenergic reuptake inhibitory mechanism may contribute to a possible opiate-sparing effect. Also, the minimal serotonergic effects may avoid the potential pronociceptive facilitatory effects of serotonin.

There is minimal protein binding and no active metabolites, resulting in a lower potential for pharmacokinetic drug–drug interactions or accumulation in patients with impaired renal or hepatic function. Furthermore, both pharmacological effects of tapentadol in large part reside within the parent molecule and do not require metabolic activation. Thus, the relative contribution of the two mechanisms of action does not vary during metabolic transformation of the primary enantiomer [72].

Tapentadol has demonstrated efficacy in preclinical animal models of inflammatory and neuropathic pain [74, 75], including models of diabetic neuropathy pain [74].

The drug was initially formulated in immediate-release form for acute pain and is now also available as an extended-release formulation. The immediate-release formulation was approved for use by the U.S. FDA in 2009 as a Schedule II analgesic. The extended-release formulation was approved for chronic pain use in 2011 and for neuropathic pain associated with diabetic peripheral neuropathy in 2012.

The approvals were supported by a number of studies in acute and chronic pain. For example, in a randomized blinded phase 3 trial of patients with acute moderate-to-severe pain after bunionectomy, immediate-release tapentadol (50, 75, and 100 mg) and immediate-release oxycodone hydrochloride (15 mg) were significantly superior to placebo on measures of pain intensity. Tapentadol (100 mg) had a lower incidence of gastrointestinal adverse events than did oxycodone hydrochloride [76]. A second postbunionectomy study showed similar results. Tapentadol has also demonstrated efficacy in acute, severe postoperative dental pain [77, 78].

Clinical studies in chronic pain conditions include uncontrolled osteoarthritis pain in the hip or knee, low back pain, and pain due to diabetic peripheral neuropathy [77, 78]. Extended-release tapentadol was approved by U.S. regulatory authorities for the treatment of neuropathic pain associated with diabetes on the basis of data from two randomized-withdrawal, placebo-controlled phase 3 trials. In one reported trial, 588 patients with an at least 3-month history of opioid or nonopioid use for neuropathy and a pain score of at least 5 on a 0–10 numeric rating scale were titrated to an optimal dose of tapentadol (100–250 mg bid) during a 3-week open-label phase. Patients who had at least a one-point reduction in pain intensity during the open label phase were randomized to the optimal fixed dose of tapentadol or placebo for an additional 12 weeks. Tapentadol-treated patients experienced significantly better pain control, as compared with those who switched to placebo (change in average pain intensity from the start of double-blind treatment to week 12 was −1.3 (95 % confidence interval, −1.70 to −0.92; $p<.001$, tapentadol ER vs. placebo). The most common treatment-emergent adverse events occurring during double-blind treatment with tapentadol ER in this trial included nausea, anxiety, diarrhea, and dizziness [79••].

Taken together, the data from chronic pain studies, including those with an active opioid comparator, suggest that the drug is efficacious and has an efficacy comparable to that of other opioids, with a lower incidence of adverse events, particularly those affecting the gastrointestinal tract. Additional head-to-head comparator studies with nonopioid neuropathic pain therapeutic agents and long-term studies are necessary to define the place of this drug in the treatment of neuropathic pain due to diabetic peripheral neuropathy.

As with all opioids, pretreatment risk–benefit assessment and ongoing risk management strategies should be implemented prior to and during therapy [80, 81].

Gene Therapy

Gene therapy, an intervention that supplies disease-modifying genetic material to restore or improve function, is playing a growing role in neurotherapeutics [82, 83••]. The development of sophisticated gene delivery vehicles based on viral and nonviral vectors has facillitated the successful application of this approach in preclinical, animal pain models. These vectors permit delivery of genes that encode potential therapeutic products such as opioids, neurotransmitters, neurotrophins, immune modulators, and antisense RNA to genes that play a role in pain modulation [82, 84, 85].

Nonviral plasmids are the simplest vector for transport of DNA into the cell nucleus. Delivery methods for plasmids

include the injection of naked plasmid DNA, liposome or nanoparticle-mediated delivery, and physical methods. These methods are the least susceptible to complications but yield low transduction efficiency and have a short duration of transgene expression [82, 84, 85]. Most commonly used viral vectors include those based on adenovirus, adeno-associated virus, lentivirus, retrovirus, and herpes simplex viruses. These viral vectors differ with respect to their safety, pathogenicity, immunogenicity, long-term gene expression capability, delivery capacity, target specificity, ease of elimination, and propensity for mutagenicity [82, 84, 85].

Gene therapy offers several potential advantages with respect to pain therapy. It may allow for the continuous, focused production of analgesic molecules, thereby potentially minimizing the likelihood of off-target effects. The neurotrophism of herpes simplex virus (HSV) renders it a promising candidate for the treatment of pain disorders. Primary afferent neurons are the natural target of this viral vector that maintains lifelong residency in the nucleus of infected neurons [86]. The viral vector infects epithelial cells or neurons directly after subcutaneous injection or topical application. The vector penetrates peripheral afferent terminals and is transported retrogradely to the cell bodies of the dorsal root sensory and trigeminal ganglia. The virus displays lifelong persistence in sensory neurons in a nonintegrated state that mimics viral latency. In preclinical studies of rodent pain models, HSV-based vectors expressing opioid peptides, glutamic acid decarboxylase, and antiinflammatory peptides have demonstrated efficacy in reducing peripheral and central pain. Similarly, vectors expressing neurotrophic factors, including nerve growth factor (NGF), neurotrophin-3, vascular endothelial growth factor, and erythropoietin, have been shown to prevent the progression of neuropathy in preclinical models of toxic neuropathy and diabetic neuropathy [83••, 85].

Clinical studies of gene therapy for pain in humans are in the early stages. The first human clinical trial of gene therapy for neuropathic pain was a dose-escalation, phase I investigation of 10 subjects with intractable focal pain caused by cancer. A replication-defective HSV-based vector expressing human preproenkephalin was injected intradermally into the dermatome(s) corresponding to the radicular distribution of pain. Subjects had moderate to severe intractable pain despite treatment with >200 mg/day of morphine (or equivalent). Treatment was well tolerated. No study agent-related serious adverse events were observed at any point in the study. Subjects in the middle- and high-dose cohorts reported pain relief as assessed by numeric rating scale and the McGill pain questionnaire short form, suggesting a dose response; however, there was no placebo or control group in the study [87•]. A preliminary report of results from a phase II, placebo-controlled trial using this same intervention in patients with cancer pain showed no difference in average pain scores between those patients who received a single dose of treatment and those who received placebo.

Hepatocyte growth factor is a mesenchymal-derived cytokine with angiogenic and antifibrotic activities [88]. There is some evidence that hepatocyte growth factor is neurotrophic for peripheral sensory, sympathetic, and motor neurons and promotes neuronal survival and axonal growth [89, 90].

The safety of intramuscular injections of plasmid DNA expressing two isoforms of hepatocyte growth factor was investigated in 12 patients with painful diabetic peripheral neuropathy. In an open-label, uncontrolled study, patients received three dose tiers separated by 2 weeks. There were no serious adverse events. A dose-related improvement in pain score was using a visual analog scale was observed; however, this finding is of limited significance in an open-label study without a control group [91].

A phase 2 randomized, double-blind, placebo-controlled study in patients with painful diabetic peripheral neuropathy is in progress (http://clinicaltrials.gov/ct2/show/NCT01475786) . Improvement in pain score is the primary efficacy endpoint in this 6-month study (the change in the average 24-h pain score between baseline and the 6-month follow); however, given the mechanism of action of this agent, a disease-modifying endpoint seems more appropriate.

Neurotrophins: Anti-Nerve Growth Factor Molecules

NGF is a neurotrophin that modulates the growth maintenance and survival of small-fiber and autonomic neurons. NGF acts through two cell-surface receptors, the high-affinity tropomyosin-related kinase A (Trk A) receptor, a tyrosine kinase, and the low-affinity 75-kDa, p75 receptor, a member of the tumor necrosis factor receptor family [92].

Mutations in humans and animal models have defined the role of NGF in pain [93]. In humans and animals with loss of function mutations in NGF or Trk A, there is a loss of sensory and sympathetic neurons, with associated impairment in pain perception and autonomic function [94, 95]. Mice lacking NGF or Trk A developed severe sensory and autonomic neuropathies that led to death approximately 1 month after birth [96, 97]. Humans with mutations in the Trk A gene develop insensitivity to noxious stimuli and anhidrosis—a disorder known as hereditary sensory and autonomic neuropathy (HSAN) IV or congenital insensitivity to pain with anhidrosis. Concomitant clinical features include episodic fevers, mental retardation, self-mutilation, bone fractures, impaired immunity, and poor wound healing [98, 99]. Humans with mutations on the NGFβ gene that encodes NGF, a disorder known as HSAN V, develop impaired pain perception (most notably, deep pain), with associated fractures, trophic injury, and joint destruction [94, 100].

A body of evidence has accumulated characterizing the role of NGF in pain modulation [101]. Increased NGF levels

are present in animal models of inflammation and in humans with chronic pain states [102, 103]. NGF activates and sensitizes peripheral nociceptors, and increased expression of NGF is found locally in tissues of patients with inflammatory conditions such as arthritis, prostatitis, and pancreatitis. In animals and humans, exogenous administration of NGF causes local and systemic pain [104].

There is preclinical evidence that antibodies generated for NGF and its receptor reduce pain in preclinical animal models. These data have provided the rationale for the investigation of anti-NGF molecules for the treatment of pain in humans. Development programs exist for several anti-NGF antibodies, including tanezumab, fulranumab, REGN475, and MEDI-578. Of these molecules, tanezumab, a humanized monoclonal antibody that binds and inhibits NGF, is the best studied. The safety and analgesic efficacy of tanezumab has been investigated in several proof-of-concept human studies. In patients with osteoarthritis of the knee, treatment with tanezumab was associated with a reduction in baseline knee pain while walking of 45 %–62 %, as compared with 22 % with placebo. There was an improvement in the global assessment of therapy in the actively treated group [105••]. In chronic low back pain patients, greater proportions of patients reported ≥30 % and ≥50 % reduction in pain with tanezumab versus naproxen and placebo [106]. In a small study of patients with interstitial cystitis, the tanezumab cohort had a significant reduction in the average pain score, as compared with placebo [107].

In 2010, the FDA halted the anti-NGF development programs for all indications, with the exception of cancer pain, when reports from clinical trials emerged that the drugs may cause adverse joint-related events that necessitate joint replacement. This hold has impeded study of this class of agents in painful diabetic peripheral neuropathy

A proof-of-concept phase 2 study to determine the effectiveness and safety of tanezumab in adult patients with painful diabetic peripheral neuropathy (http://clinicaltrials.gov/ct2/show/NCT01087203) was terminated during the clinical hold for potential safety issues. A multidose 12-week, double-blind, placebo-controlled safety and efficacy study (and subsequent blinded, followed by open-label extension study) with fulranumab was also terminated due to the FDA clinical hold. Analysis of the data from the 77 of 200 planned patients who were enrolled in this study prior to the clinical hold revealed a positive dose response. A pairwise comparison between the highest dose of fulranumab and placebo showed nominal statistical significance (http://www.neurology.org/cgi/content/meeting_abstract/80/1_MeetingAbstracts/S58.002).

In March 2012, an FDA advisory panel unanimously agreed that anti-NGF drugs "showed promise as analgesics" and that clinical development could continue with close monitoring of joint-related adverse events and adequate informed consent. At present, comprehensive surveillance measures are being developed to minimize the clinical risk of this agent class. Pain associated with peripheral neuropathies, particularly those with predominantly small-fiber and autonomic pathology such as diabetes, may have unique risks and require additional surveillance measures.

Conclusion

The worldwide increase in the prevalence of diabetes, diabetic peripheral neuropathy, and neuropathic pain associated with diabetic peripheral neuropathy emphasizes the need for effective analgesic agents. However, the treatment of neuropathic pain—and in particular, the pain associated with diabetic peripheral neuropathy—continues to be a challenge. Current pharmacological approaches do not provide satisfactory pain relief in many patients. Even the most efficacious agents in clinical trials elicit 50 % pain relief in fewer than 50 % of subjects. The agents discussed in this article, in general, represent a molecular-target-based approach derived from preclinical and clinical data. This rational approach, allied with appropriate patient selection and clinical design methods, should result in more effective treatment of this growing problem.

Acknowledgment Roy Freeman has received grant support from the NIH.

Compliance with Ethics Guidelines

Conflict of Interest Roy Freeman has been a consultant for Pfizer, Eli Lilly, Abbott, Bristol-Myers-Squibb, Chelsea, GlaxoSmithKline, Sanofi-Aventis, Depomed, and Johnson & Johnson.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Daousi C, MacFarlane IA, Woodward A, Nurmikko TJ, Bundred PE, Benbow SJ. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. Diabet Med. 2004;21:976–82.
2. Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. Diabetes Care. 2006;29:1518–22.
3. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A. Neuropathic pain in diabetes, prediabetes and normal glucose

tolerance: the MONICA/KORA Augsburg Surveys S2 and S3. Pain Med. 2009;10:393–400.
4. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. Diabetes Care. 2008;31:464–9.
5. Freeman R. Pharmacotherapy of neuropathic pain. In: Simpson DM, McArthur JC, Dworkin RH, editors. Neuropathic Pain: Mechanisms, Diagnosis and Treatment. New York: Oxford University Press; 2012. p. 112–31.
6. Caterina MJ. Vanilloid receptors take a TRP beyond the sensory afferent. Pain. 2003;105:5–9.
7. Pingle SC, Matta JA, Ahern GP (2007) Capsaicin receptor: TRPV1 a promiscuous TRP channel. HandbExpPharmacol: 155–171
8. Facer P, Casula MA, Smith GD, et al. Differential expression of the capsaicin receptor TRPV1 and related novel receptors TRPV3, TRPV4 and TRPM8 in normal human tissues and changes in traumatic and diabetic neuropathy. BMCNeurol. 2007;7:11.
9. Lauria G, Morbin M, Lombardi R, et al. Expression of capsaicin receptor immunoreactivity in human peripheral nervous system and in painful neuropathies. J Peripher Nerv Syst. 2006;11:262–71.
10. Derry S, Lloyd R, Moore RA, McQuay HJ (2009) Topical capsaicin for chronic neuropathic pain in adults. CochraneDatabaseSystRev: CD007393
11. Nolano M, Simone DA, Wendelschafer-Crabb G, Johnson T, Hazen E, Kennedy WR. Topical capsaicin in humans: parallel loss of epidermal nerve fibers and pain sensation. Pain. 1999;81:135–45.
12. Simone DA, Nolano M, Johnson T, Wendelschafer-Crabb G, Kennedy WR. Intradermal injection of capsaicin in humans produces degeneration and subsequent reinnervation of epidermal nerve fibers: correlation with sensory function. J Neurosci. 1998;18:8947–59.
13. Polydefkis M, Hauer P, Sheth S, Sirdofsky M, Griffin JW, McArthur JC. The time course of epidermal nerve fibre regeneration: studies in normal controls and in people with diabetes, with and without neuropathy. Brain. 2004;127:1606–15.
14. Gibbons CH, Wang N, Freeman R. Capsaicin induces degeneration of cutaneous autonomic nerve fibers. Ann Neurol. 2010;68:888–98.
15. Wood JN, Winter J, James IF, Rang HP, Yeats J, Bevan S. Capsaicin-induced ion fluxes in dorsal root ganglion cells in culture. J Neurosci. 1988;8:3208–20.
16. Sikand P, Premkumar LS. Potentiation of glutamatergic synaptic transmission by protein kinase C-mediated sensitization of TRPV1 at the first sensory synapse. J Physiol. 2007;581:631–47.
17. Amantini C, Mosca M, Nabissi M, et al. Capsaicin-induced apoptosis of glioma cells is mediated by TRPV1 vanilloid receptor and requires p38 MAPK activation. J Neurochem. 2007;102:977–90.
18. Mason L, Moore RA, Derry S, Edwards JE, McQuay HJ. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ. 2004;328:991.
19. Bernstein JE, Korman NJ, Bickers DR, Dahl MV, Millikan LE. Topical capsaicin treatment of chronic postherpetic neuralgia. J Am Acad Dermatol. 1989;21:265–70.
20. (1992) Effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. Capsaicin Study Group. Diabetes Care 15: 159–165
21. Tandan R, Lewis GA, Badger GB, Fries TJ. Topical capsaicin in painful diabetic neuropathy. Effect on sensory function. Diabetes Care. 1992;15:15–8.
22. Low PA, Opfer-Gehrking TL, Dyck PJ, Litchy WJ, O'Brien PC. Double-blind, placebo-controlled study of the application of capsaicin cream in chronic distal painful polyneuropathy. Pain. 1995;62:163–8.
23. Watson CP, Tyler KL, Bickers DR, Millikan LE, Smith S, Coleman E. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. Clin Ther. 1993;15:510–26.
24. Ellison N, Loprinzi CL, Kugler J, et al. Phase III placebo-controlled trial of capsaicin cream in the management of surgical neuropathic pain in cancer patients. J Clin Oncol. 1997;15:2974–80.
25. Watson CP, Evans RJ. The postmastectomy pain syndrome and topical capsaicin: a randomized trial. Pain. 1992;51:375–9.
26. • Backonja M, Wallace MS, Blonsky ER, et al. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. Lancet Neurol. 2008;7:1106–12. *The first pivotal trial demonstrating efficacy of a high-concentration capsaicin patch for the treatment of postherpetic neuralgia*.
27. Backonja MM, Malan TP, Vanhove GF, Tobias JK. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomized, double-blind, controlled study with an open-label extension. Pain Med. 2010;11:600–8.
28. Irving GA, Backonja MM, Dunteman E, et al. A multicenter, randomized, double-blind, controlled study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. Pain Med. 2011;12:99–109.
29. Simpson DM, Brown S, Tobias J. Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy. Neurology. 2008;70:2305–13.
30. Kennedy WR, Vanhove GF, Lu SP, et al. A randomized, controlled, open-label study of the long-term effects of NGX-4010, a high-concentration capsaicin patch, on epidermal nerve fiber density and sensory function in healthy volunteers. J Pain Off J Am Pain Soc. 2010;11:579–87.
31. Jancso N, Jancso-Gabor A, Szolcsanyi J. Direct evidence for neurogenic inflammation and its prevention by denervation and by pretreatment with capsaicin. Br J Pharmacol Chemother. 1967;31:138–51.
32. Schuller TB, Hermann K, Baron R. Quantitative assessment and correlation of sympathetic, parasympathetic, and afferent small fiber function in peripheral neuropathy. J Neurol. 2000;247:267–72.
33. Low VA, Sandroni P, Fealey RD, Low PA. Detection of small-fiber neuropathy by sudomotor testing. Muscle Nerve. 2006;34:57–61.
34. Parkhouse N, Le Quesne PM. Impaired neurogenic vascular response in patients with diabetes and neuropathic foot lesions. N Engl J Med. 1988;318:1306–9.
35. Berghoff M, Kilo S, Hilz MJ, Freeman R (2006) Differential impairment of the sudomotor and nociceptor axon-reflex in diabetic peripheral neuropathy. Muscle Nerve
36. Boulton AJ, Kirsner RS, Vileikyte L. Clinical practice. Neuropathic diabetic foot ulcers. N Engl J Med. 2004;351:48–55.
37. Abbott CA, Carrington AL, Ashe H, et al. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabet Med. 2002;19:377–84.
38. Abbott CA, Vileikyte L, Williamson S, Carrington AL, Boulton AJ. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. Diabetes Care. 1998;21:1071–5.
39. Young MJ, Breddy JL, Veves A, Boulton AJ. The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds. A prospective study. Diabetes Care. 1994;17:557–60.

40. • Brederson JD, Kym PR, Szallasi A (2013) Targeting TRP channels for pain relief. Eur J Pharmacol. *Review of current TRP channel therapeutic approaches*.
41. Chen J, Joshi SK, DiDomenico S, et al. Selective blockade of TRPA1 channel attenuates pathological pain without altering noxious cold sensation or body temperature regulation. Pain. 2011;152:1165–72.
42. Andrade EL, Meotti FC, Calixto JB. TRPA1 antagonists as potential analgesic drugs. Pharmacol Ther. 2012;133:189–204.
43. Kremeyer B, Lopera F, Cox JJ, et al. A gain-of-function mutation in TRPA1 causes familial episodic pain syndrome. Neuron. 2010;66:671–80.
44. Waxman SG, Cummins TR, Dib-Hajj S, Fjell J, Black JA. Sodium channels, excitability of primary sensory neurons, and the molecular basis of pain. Muscle Nerve. 1999;22:1177–87.
45. Catterall WA, Goldin AL, Waxman SG. International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels. Pharmacol Rev. 2005;57:397–409.
46. Hains BC, Saab CY, Klein JP, Craner MJ, Waxman SG. Altered sodium channel expression in second-order spinal sensory neurons contributes to pain after peripheral nerve injury. J Neurosci. 2004;24:4832–9.
47. Craner MJ, Klein JP, Renganathan M, Black JA, Waxman SG. Changes of sodium channel expression in experimental painful diabetic neuropathy. Ann Neurol. 2002;52:786–92.
48. Dib-Hajj SD, Fjell J, Cummins TR, et al. Plasticity of sodium channel expression in DRG neurons in the chronic constriction injury model of neuropathic pain. Pain. 1999;83:591–600.
49. Black JA, Cummins TR, Plumpton C, et al. Upregulation of a silent sodium channel after peripheral, but not central, nerve injury in DRG neurons. J Neurophys. 1999;82:2776–85.
50. Devor M, Govrin-Lippmann R, Angelides K. Na + channel immunolocalization in peripheral mammalian axons and changes following nerve injury and neuroma formation. J Neurosci. 1993;13:1976–92.
51. Devor M, Wall PD, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. Pain. 1992;48:261–8.
52. • Fischer TZ, Waxman SG. Familial pain syndromes from mutations of the NaV1.7 sodium channel. Ann NY Acad Sci. 2010;1184:196–207. *Review of the inherited pain syndromes associated with mutations in the NaV1.7 sodium channel.*
53. Dib-Hajj SD, Rush AM, Cummins TR, et al. Gain-of-function mutation in Nav1.7 in familial erythromelalgia induces bursting of sensory neurons. Brain. 2005;128:1847–54.
54. Nilsen KB, Nicholas AK, Woods CG, Mellgren SI, Nebuchennykh M, Aasly J. Two novel SCN9A mutations causing insensitivity to pain. Pain. 2009;143:155–8.
55. Cox JJ, Reimann F, Nicholas AK, et al. An SCN9A channelopathy causes congenital inability to experience pain. Nature. 2006;444:894–8.
56. Cregg R, Momin A, Rugiero F, Wood JN, Zhao J. Pain channelopathies. J Physiol. 2010;588:1897–904.
57. •• Faber CG, Hoeijmakers JG, Ahn HS, et al. Gain of function Na(V) 1.7 mutations in idiopathic small fiber neuropathy. Ann Neurol. 2012;71:26–39. *First report suggestion that gain of functions NaV1.7 mutations may be present in idiopathic small-fiber neuropathies*.
58. Hoeijmakers JG, Faber CG, Lauria G, Merkies IS, Waxman SG. Small-fibre neuropathies-advances in diagnosis, pathophysiology and management. Nat Rev Neurol. 2012;8:369–79.
59. Chattopadhyay M, Zhou Z, Hao S, Mata M, Fink DJ. Reduction of voltage gated sodium channel protein in DRG by vector mediated miRNA reduces pain in rats with painful diabetic neuropathy. Molecular pain. 2012;8:17.
60. Chattopadhyay M, Mata M, Fink DJ. Continuous delta-opioid receptor activation reduces neuronal voltage-gated sodium channel (NaV1.7) levels through activation of protein kinase C in painful diabetic neuropathy. J Neurosci Off J Soc Neurosci. 2008;28:6652–8.
61. Nassar MA, Baker MD, Levato A, et al. Nerve injury induces robust allodynia and ectopic discharges in Nav1.3 null mutant mice. Mol Pain. 2006;2:33.
62. Nassar MA, Levato A, Stirling LC, Wood JN. Neuropathic pain develops normally in mice lacking both Na(v)1.7 and Na(v)1.8. Mol Pain. 2005;1:24.
63. Ossipov MH, Lai J, King T, et al. Antinociceptive and nociceptive actions of opioids. J Neurobiol. 2004;61:126–48.
64. Pasternak GW. Molecular insights into mu opioid pharmacology: From the clinic to the bench. Clin J Pain. 2010;26 Suppl 10:S3–9.
65. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: A randomized controlled trial. Neurology. 2003;60:927–34.
66. Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Neurology. 1998;50:1837–41.
67. Watson CP, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain. 2003;105:71–8.
68. Raja SN, Haythornthwaite JA, Pappagallo M, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology. 2002;59:1015–21.
69. Rowbotham MC, Twilling L, Davies PS, Reisner L, Taylor K, Mohr D. Oral opioid therapy for chronic peripheral and central neuropathic pain. N Engl J Med. 2003;348:1223–32.
70. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med. 2005;352:1324–34.
71. Gassner M, Ruscheweyh R, Sandkuhler J. Direct excitation of spinal GABAergic interneurons by noradrenaline. Pain. 2009;145:204–10.
72. Tzschentke TM, Christoph T, Kogel B, et al. (−)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel mu-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. J Pharmacol Exp Ther. 2007;323:265–76.
73. Bee LA, Bannister K, Rahman W, Dickenson AH. Mu-opioid and noradrenergic alpha(2)-adrenoceptor contributions to the effects of tapentadol on spinal electrophysiological measures of nociception in nerve-injured rats. Pain. 2011;152:131–9.
74. Christoph T, De Vry J, Tzschentke TM. Tapentadol, but not morphine, selectively inhibits disease-related thermal hyperalgesia in a mouse model of diabetic neuropathic pain. Neurosci Lett. 2010;470:91–4.
75. Schroder W, Vry JD, Tzschentke TM, Jahnel U, Christoph T. Differential contribution of opioid and noradrenergic mechanisms of tapentadol in rat models of nociceptive and neuropathic pain. Eur J Pain (London, England). 2010;14:814–21.
76. Daniels SE, Upmalis D, Okamoto A, Lange C, Haeussler J. A randomized, double-blind, phase III study comparing multiple doses of tapentadol IR, oxycodone IR, and placebo for postoperative (bunionectomy) pain. Curr Med Res Opin. 2009;25:765–76.
77. Hoy SM. Tapentadol extended release: in adults with chronic pain. Drugs. 2012;72:375–93.
78. Hartrick CT, Rozek RJ. Tapentadol in pain management: a mu-opioid receptor agonist and noradrenaline reuptake inhibitor. CNS drugs. 2011;25:359–70.
79. •• Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-

controlled trial. Curr Med Res Opin. 2011;27:151–62. *One of two pivotal randomized-withdrawal design trials demonstrating the efficacy of tapentadol ER in the treatment of painful diabetic peripheral neuropathy.*
80. Katz NP, Adams EH, Benneyan JC, et al. Foundations of opioid risk management. Clin J Pain. 2007;23:103–18.
81. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. Ann Intern Med. 2007;146:116–27.
82. Fink DJ, Wolfe D. Gene Therapy for Pain: A Perspective. Pain Manag. 2011;1:379–81.
83. •• Simonato M, Bennett J, Boulis NM, et al. (2013) Progress in gene therapy for neurological disorders. Nature reviews Neurology *Overview of current issues and strategies in gene therapy for neurological disorders*.
84. Wolfe D, Mata M, Fink DJ. Targeted drug delivery to the peripheral nervous system using gene therapy. Neurosci Lett. 2012;527:85–9.
85. Goins WF, Cohen JB, Glorioso JC. Gene therapy for the treatment of chronic peripheral nervous system pain. Neurobiol Dis. 2012;48:255–70.
86. Glorioso JC, Fink DJ. Herpes vector-mediated gene transfer in the treatment of chronic pain. Mol Ther Clin J Am Society Gene Ther. 2009;17:13–8.
87. • Fink DJ, Wechuck J, Mata M, et al. Gene therapy for pain: results of a phase I clinical trial. Ann Neurol. 2011;70:207–12. *First gene therapy trial for neuropathic pain.*
88. Matsumoto K, Nakamura T. Emerging multipotent aspects of hepatocyte growth factor. J Biochem. 1996;119:591–600.
89. Yang XM, Toma JG, Bamji SX, et al. Autocrine hepatocyte growth factor provides a local mechanism for promoting axonal growth. J Neurosci Off J Soc Neurosci. 1998;18:8369–81.
90. Gascon E, Gaillard S, Malapert P, et al. Hepatocyte growth factor-Met signaling is required for Runx1 extinction and peptidergic differentiation in primary nociceptive neurons. J Neurosci Off J Soc Neurosci. 2010;30:12414–23.
91. Ajroud-Driss S, Christiansen M, Allen JA, Kessler JA (2013) Phase 1/2 Open-label Dose-escalation Study of Plasmid DNA Expressing Two Isoforms of Hepatocyte Growth Factor in Patients With Painful Diabetic Peripheral Neuropathy. Molecular therapy : the journal of the American Society of Gene Therapy
92. Mantyh PW, Koltzenburg M, Mendell LM, Tive L, Shelton DL. Antagonism of nerve growth factor-TrkA signaling and the relief of pain. Anesthesiology. 2011;115:189–204.
93. Rotthier A, Baets J, Timmerman V, Janssens K. Mechanisms of disease in hereditary sensory and autonomic neuropathies. Nat Rev Neurol. 2012;8:73–85.
94. Capsoni S, Covaceuszach S, Marinelli S, et al. Taking pain out of NGF: a "painless" NGF mutant, linked to hereditary sensory autonomic neuropathy type V, with full neurotrophic activity. PLoSOne. 2011;6:e17321.
95. Obata K, Katsura H, Sakurai J, et al. Suppression of the p75 neurotrophin receptor in uninjured sensory neurons reduces neuropathic pain after nerve injury. J Neurosci Off J Soc Neurosci. 2006;26:11974–86.
96. Smeyne RJ, Klein R, Schnapp A, et al. Severe sensory and sympathetic neuropathies in mice carrying a disrupted Trk/NGF receptor gene. Nature. 1994;368:246–9.
97. Crowley C, Spencer SD, Nishimura MC, et al. Mice lacking nerve growth factor display perinatal loss of sensory and sympathetic neurons yet develop basal forebrain cholinergic neurons. Cell. 1994;76:1001–11.
98. Indo Y. Genetics of congenital insensitivity to pain with anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV. Clinical, biological and molecular aspects of mutations in TRKA(NTRK1) gene encoding the receptor tyrosine kinase for nerve growth factor. Clin Auton Res. 2002;12 Suppl 1:I20–32.
99. Indo Y, Tsuruta M, Hayashida Y, et al. Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat Genet. 1996;13:485–8.
100. Houlden H, King RH, Hashemi-Nejad A, et al. A novel TRK A (NTRK1) mutation associated with hereditary sensory and autonomic neuropathy type V. Ann Neurol. 2001;49:521–5.
101. McMahon SB, Bennett DL, Priestley JV, Shelton DL. The biological effects of endogenous nerve growth factor on adult sensory neurons revealed by a trkA-IgG fusion molecule. Nat Med. 1995;1:774–80.
102. McMahon SB. NGF as a mediator of inflammatory pain. Philos Trans R Soc B-Biol Sci. 1996;351:431–40.
103. Woolf CJ, Safieh-Garabedian B, Ma QP, Crilly P, Winter J. Nerve growth factor contributes to the generation of inflammatory sensory hypersensitivity. Neuroscience. 1994;62:327–31.
104. Gerber RK, Nie H, Arendt-Nielsen L, Curatolo M, Graven-Nielsen T. Local pain and spreading hyperalgesia induced by intramuscular injection of nerve growth factor are not reduced by local anesthesia of the muscle. Clin J Pain. 2011;27:240–7.
105. •• Lane NE, Schnitzer TJ, Birbara CA, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. N Engl J Med. 2010;363:1521–31. *Proof-of-concept trial using antibody to NGF to treat pain due to osteoarthritis*.
106. Ackermann PW (2012) Katz et al., efficacy and safety of tanezumab in the treatment of chronic low back pain [Pain 2011;152:2248–2258] and Hill, blocking the effects of NGF as a route to safe and effective pain relief - fact or fancy? [Pain 2011;152:2200–2201]. Pain 153: 1128–1129; author reply 1129–1131
107. Evans RJ, Moldwin RM, Cossons N, Darekar A, Mills IW, Scholfield D. Proof of concept trial of tanezumab for the treatment of symptoms associated with interstitial cystitis. J Urol. 2011;185:1716–21.