mhc MENTAL HEALTH CLINICIAN

REVIEW OF DRUGS/PHARMACOTHERAPY Open Access

Pharmacologic basis for the use of selective norepinephrine reuptake inhibitors for the treatment of neuropathic pain conditions

Michael Webster, PharmD[1]

How to Cite: Webster M. Pharmacologic basis for the use of selective norepinephrine reuptake inhibitors for the treatment of neuropathic pain conditions. Ment Health Clin [Internet]. 2015;5(6):284-8. DOI: 10.9740/mhc.2015.11.284.

Abstract

Introduction: This article will review the pharmacologic and clinical evidence supporting the use of selective norepinephrine reuptake inhibitors, most notably atomoxetine, for the treatment of neuropathic pain states. Many medications initially marketed for psychiatric indications have gained widespread use for their analgesic properties after additional research.

Methods: In search of alternative treatments for neuropathic pain, current guidelines, published reviews, and primary literature, including both rodent and human trials, were reviewed.

Results and Discussion: The first group of medications to gain widespread use in pain management was the tricyclic antidepressants. As further research was completed and serotonin norepinephrine reuptake inhibitors began to be utilized for their analgesic properties, a growing body of evidence began to indicate that the analgesic properties of these medications were primarily due to the blockade of norepinephrine reuptake with serotonin playing only a minimal role.

Keywords: atomoxetine, neuropathic pain, off-label use

[1] (Corresponding author) Clinical Pharmacist, Northern Navajo Medical Center, Indian Health Service, Shiprock, NM, michael.webster@IHS.gov

Introduction

The treatment of neuropathic pain conditions, such as fibromyalgia and diabetic neuropathy, generally relies on a small number of medication classes. The largest of these classes are drugs that act by blocking the reuptake of serotonin and norepinephrine. These medications include serotonin norepinephrine reuptake inhibitors (SNRIs), such as duloxetine, and tricyclic antidepressants (TCAs), such as amitriptyline, nortriptyline, and others.

Methods

Although SNRIs and TCAs both inhibit reuptake of serotonin and norepinephrine, a number of studies now indicate that the analgesic effects of these drugs are dependent on the inhibition of norepinephrine reuptake alone with the serotonin component contributing far less to the analgesic effect.[1-4] If this is indeed the case, a pharmacologic argument could be made for the use of selective norepinephrine reuptake inhibitors (NRIs), such as atomoxetine, for the treatment of neuropathic pain conditions. If proven, it would provide a valuable expansion of the pharmacologic arsenal used to treat these conditions. An extensive literature review was conducted searching Pubmed and Embase for evidence of the contribution of norepinephrine reuptake inhibition to the analgesic properties of SNRIs, TCAs, and NRIs in neuropathic pain states.

Results

Before beginning this review, several definitions must be clarified. In reviewing the literature, it became clear that there was no consistent definition for what constituted a SNRI or what a selective NRI was. For example, the

TABLE: Relative binding affinities for serotonin reuptake transporter and norepinephrine reuptake transporter of select medications

Drug	NE Reuptake Inhibition MIC, nmol/L	5-HT Reuptake Inhibition MIC, nmol/L	NE:5HT Selectivity Ratio	Pharmacologic Class	Source
Atomoxetine	5	77	0.07:1	selective NRI	Bymaster et al[21]
Milnacipran	68	151	0.45:1	SNRI	Vaishnavi et al[22]
Duloxetine	20	3.7	5.4:1	SNRI	Vaishnavi et al[22]
Venlafaxine	1420	145	9.79:1	SNRI	Vaishnavi et al[22]
Citalopram	8690	19	457.37:1	SSRI	Vaishnavi et al[22]
Amitriptyline	63	67	0.94:1	TCA	Vaishnavi et al[22]
Nortriptyline	8.3	317	0.03:1	TCA	Vaishnavi et al[22]

NRI = norepinephrine reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

reviews published by Hartrick and Fishbain both considered various tricyclic antidepressants as NRIs based on their binding affinities.[4,5] For the purpose of this paper, selective NRIs will only include drugs that have a binding affinity for the norepinephrine reuptake transporter 10 times as high as that for the serotonin reuptake transporter. Given the wide range of other receptors TCAs interact with, they will continue to be considered a unique class.

The drugs listed in the Table were chosen because they represent a broad spectrum of medications. Some of these medications have been proven efficacious in treating neuropathic pain conditions and are frequently used for these indications, and others have been found to be ineffective. Specifically, duloxetine, milnacipran, amitriptyline, and nortriptyline are proven treatments for neuropathic pain conditions, and venlafaxine has been found to be efficacious only at higher doses.[6] Citalopram has been found to be ineffective and have little role in the treatment of pain conditions outside the treatment of concomitant depressive disorders. This is important because it directly follows the selectivity of the drugs for norepinephrine as shown in the Figure; agents with higher norepinephrine selectivity are effective, venlafaxine with intermediate selectivity is effective only at higher doses, and those with low norepinephrine selectivity are not.

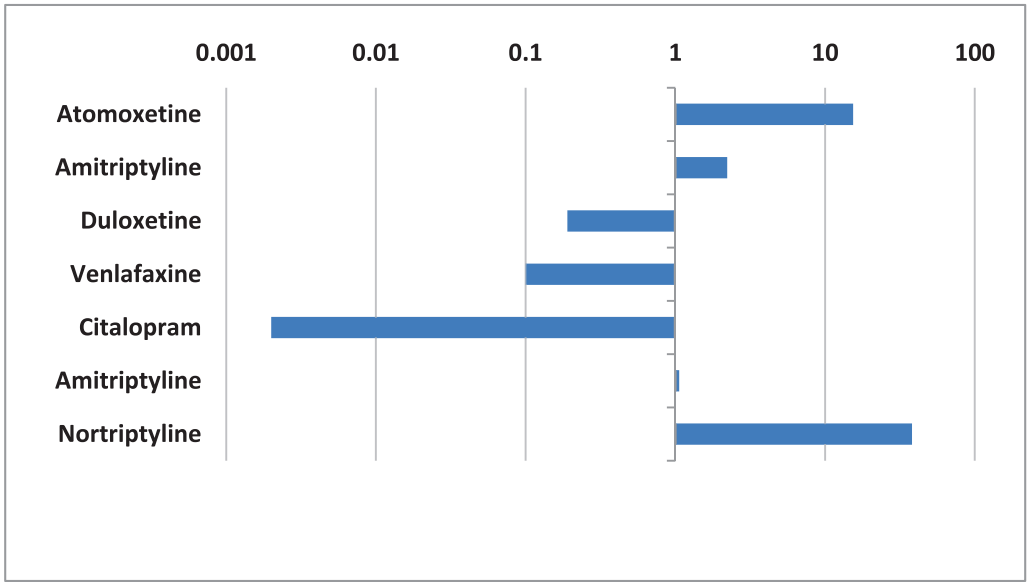

FIGURE: Relative selectivity of inhibition of the 5-HT reuptake transporter and the norepinephrine reuptake transporter. Value calculated by dividing the Ki for the serotonin transporter (SERT) by the Ki for the norepinephrine transporter (NERT). Values > 1 indicate greater selectivity for NERT, values = 1 indicate equal inhibition, and < 1 indicates electivity for SERT. Given the wide range of values, graph is plotted on a logarithmic scale

In addition to the evidence provided from drug-binding affinity, a number of clinical studies in both rodent and human models of neuropathic pain show that inhibition of norepinephrine reuptake is critical for the efficacy of these medications in the treatment of neuropathic pain.[1-3]

Venlafaxine uniquely demonstrates the criticality of norepinephrine reuptake in the analgesic properties of reuptake inhibitors by its dose-dependent analgesic effects. Currently, the professional opinion on venlafaxine's analgesic properties is mixed. The 2013 guideline on the pharmacological management of neuropathic pain by the National Institute for Health and Care Excellence specifically recommends against the routine use of venlafaxine.[7] On the other hand, the American Academy of Neurology's 2011 guideline on the treatment of painful diabetic neuropathy recommends amitriptyline, duloxetine, and venlafaxine with a B grade of evidence and notes that there is insufficient evidence to recommend any agent over the others.[8]

This reasoning behind this mixed guidance can possibly be explained in part by the pharmacologic properties of venlafaxine. Unlike duloxetine, which has a high affinity for the norepinephrine transporter and has been shown to be efficacious throughout its standard dosing range,[9] venlafaxine has been shown in both in vitro and in vivo studies to selectively inhibit serotonin reuptake at lower doses and inhibit reuptake of both serotonin and norepinephrine only at higher doses.[9-11] This correlation is further evidenced by Rowbothman et al, who showed venlafaxine only had significant analgesic properties at the upper end of its standard dosing range.[6] This study randomized 244 adults with diabetic neuropathy to receive placebo, venlafaxine ER 75 mg/d, or venlafaxine ER 150 to 225 mg/d. The patients randomized to high-dose venlafaxine showed significantly greater pain relief than both placebo and low-dose venlafaxine.

In addition, two other publications, Fishbain et al and Leventhal et al, concluded that selective NRIs would indeed be effective.[3,12] However, it is important to note a caveat in their conclusions. They conclude that blockade of norepinephrine transporters is indeed critical for analgesic activity and plays a significantly larger role than that of serotonin. However, they also state that blockade of serotonin reuptake augments the analgesic effects and produces a higher level of analgesia than a selective NRI alone would produce. It should be noted that no study to date has used atomoxetine as the studied selective NRI to treat neuropathic pain. Rather, maprotiline and reboxetine have been studied, neither of which is approved for human use in the United States.

Limited data exist on the role of other selective NRIs, such as maprotiline and reboxetine, in management of neuropathic pain states. Maprotiline has been found to treat pain from post-herpetic neuralgia significantly better than placebo.[13] Maprotiline has also been tested against amitriptyline and clomipramine and consistently found effective but to a lesser extent than the comparator.[13-15] It is important note that all three studied populations had significant rates of concomitant depressive disorder, and in two of the studies, improvement in depressive symptomatology was the primary outcome, preventing firm conclusions from being extrapolated to nondepressed patients.

Reboxetine also has a very limited set of data regarding its efficacy in pain management. Krell et al used 3 case reports to support reboxetine's analgesic properties; however, all cases were drawn from trials of reboxetine in depressed patients with pain as a secondary outcome only.[16] Although rodent models demonstrate analgesic efficacy of reboxetine, it is debatable whether this effect is due primarily to norepinephrine reuptake inhibition or secondary mechanisms.

Discussion

Given the difficulties of treatment of neuropathic pain, such as only partial pain relief with any single agent frequently resulting in the use of several medications, the ability to use a selective NRI for treatment of neuropathic pain would present a unique treatment option. Although currently there are no data to support comparable efficacy between atomoxetine and SNRIs, the hypothesis that norepinephrine reuptake inhibition alone is sufficient for analgesic efficacy in neuropathic pain implies that atomoxetine would offer an effective and potentially more tolerable treatment option for neuropathic pain. Selective NRIs could avoid many of the drawbacks of dual reuptake inhibitors, such as reduced rates of anticholinergic side effects compared to TCAs and sexual side effects compared to SNRIs, as well as reduced risk of drug interactions, such as those increasing the risk for serotonin syndrome.

Currently, no research has been conducted to assess the potential use of atomoxetine for the treatment of neuropathic pain syndromes. Eli Lilly, the manufacture of atomoxetine, was contacted in October of 2014 about the availability of any information on this potential indication; the response stated that Eli Lilly had no research data to provide. Subsequently, an extensive literature review was conducted searching Pubmed and Embase. Only two published articles specifically addressed the use of atomoxetine in fibromyalgia.

The first case report by Vorobeychik et al specifically details a 65-year-old female with both ADHD inadequately

treated with stimulant therapy and fibromyalgia that had not responded to treatment with amitriptyline, topical lidocaine, oxycodone, diazepam, metaxalone, ibuprofen, and gabapentin.[19] The patient was placed on atomoxetine in an attempt to gain better control of her ADHD, but the patient subsequently saw a 60% improvement in her average 24-hour fibromyalgia pain score from a 10/10 to 4/10. The patient also showed marked improvement in functional status with specific improvements in daily activities, ability to sleep, mood impacted by pain, ability for self care, and appetite. Although effective for the patient's fibromyalgia, the atomoxetine also aided the patient by providing an improvement of her ADHD. The patient had been stably treated for 10 months at time of publication.

The second case series was by Berigan in the Canadian Journal of Psychiatry. This case series details two patients both diagnosed with fibromyalgia.[20] One patient had a history of major depression treated with sertraline and the other dysthymic disorder treated with escitalopram. Neither patient desired to attempt a trial of an SNRI in place of their current SSRI, and combination therapy was ruled too dangerous. Patient 1 consented to a trial of atomoxetine started at 40 mg and titrated to 80 mg after 1 week. Over the next 3 weeks, pain levels decreased; the patient was able to return to work full time and began exercising regularly. Patient 2 was initially given a trial of amitriptyline but discontinued after 2 weeks due to intolerable sedation and dry mouth. A trial of atomoxetine was started at 40 mg and increased to 120 mg over 1 month. By 6 months, the patient had shown marked improvement and had returned to work full time.

Given the limited data available, it may be premature to engage in a full-scale randomized controlled trial despite the placement of this method of research at the pinnacle of clinical investigation. More appropriate at this point would be a series of case studies using atomoxetine in select patients, such as those with concomitant ADHD or treatment refractory neuropathic pain states. With continued positive findings, use of atomoxetine for this indication could potentially continue to expand.

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