

Is There a Place for β -Mimetics in Clinical Management of Neuropathic Pain? Salbutamol Therapy in Six Cases

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THE Adrenergic system, because of its reported implication in pain mechanisms, may be a potential target for chronic pain treatment. A genetic polymorphism of catechol-*O*-methyltransferase, an enzyme that metabolizes catecholamines, is related with higher pain perception¹ and persistent pain conditions because patients with higher pain sensitivity are more likely to develop chronic pain conditions.² Moreover, catechol-*O*-methyltransferase inhibition increases pain sensitivity through augmented catecholamines and activation of β -adrenergic (β -AR) receptors.³ Furthermore, a polymorphism of β_2 -adrenoceptors (β_2 -AR) has been associated with the risk for developing musculoskeletal pain disorders.⁴ In agreement, clinical studies reported that β -AR antagonists were effective in chronic musculoskeletal pain conditions, such as fibromyalgia or temporomandibular disorder.^{5,6} This effect on myalgic pain was observed in patients with altered sympathetic nervous function.^{6,7}

In addition to musculoskeletal pain disorders, neuropathic pain is another major type of chronic pain. Neuropathic pain arises as a direct consequence of a lesion or a disease affecting the somatosensory system.⁸ The prevalence of neuropathic pain has been reported to be around 6.9 and

8.2% in two large prevalence studies, and the annual incidence rate was estimated at 1%.^{9–11} Even though patients with neuropathic symptoms are rather frequent, neuropathic pain is often challenging to treat and is generally resistant to commonly used therapeutics.¹² Treatment difficulties may be due to various underlying pathophysiologic mechanisms. Indeed, neuropathic pain can be initiated not only by various diseases such as diabetes or cancer but also by trauma, post-surgical injuries, or drug treatment of cancer or human immunodeficiency virus infection.^{9,12}

Currently, antidepressants are one of the first-line treatment options in neuropathic pain management.^{8,12} These drugs are indirect adrenergic agonists because they act through the blockade of aminergic reuptake sites and thus increase endogenous levels of noradrenaline. Recent studies on the action mechanisms of antidepressants in neuropathic pain revealed the critical role played by β_2 -AR.^{13,14} The absence or blockade of β_2 -ARs suppresses the antiallodynic effects of a chronic antidepressant treatment in a neuropathic pain model.^{13,14} Interestingly, preclinical studies have also reported that the chronic direct stimulation of β_2 -ARs by agonists can alleviate neuropathic pain symptoms in a murine neuropathic pain model,^{15–17} whereas a β -AR antagonist had no effect.^{14,16} Thus, these findings differ from what was observed in musculoskeletal pain.

In this report, we show that the use of salbutamol, a short-acting β_2 -AR agonist, provided satisfying symptom management in six patients with severe neuropathic pain resistant to previous therapy.

CASE REPORTS

Six patients with severe neuropathic symptoms were referred to the pain clinic. Four men and two women, average age of 58.8 yr, were referred to our clinic for an average of 10 months. The symptoms in one patient were initiated by lumbar radiculopathy at levels L4–L5 (case 1), and one of the patients had bilateral lumbar spinal stenosis (case 5). The causes of neuropathic pain were traumatic in two patients (cases 2 and 4). In the two latter patients, neuropathic pain was due to lung cancer (cases 3 and 6). All patients had inadequate pain relief with previous therapies, including tricyclic antidepressants, nonsteroidal antiinflammatory drugs, gabapentin, pregabalin, opioids, and myorelaxants. In addition, two patients previously received therapies such as acupuncture and physical therapy other than medical treatment. The details of patient characteristics and the background of neuropathic pain are summarized in table 1.

After the routine assessment and physical examination of patients, we documented the pain intensity by visual analog pain scale and the accompanying neuropathic symptoms. The patients had no contraindication for the use of β_2 -AR agonist

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drugs. We stopped all previously used medications (table 1), except for the two patients with lung cancer who were still receiving their ongoing opioid treatment during salbutamol treatment. Then, the patients started to receive 4 mg salbutamol sustained release formula orally daily. All patients were contacted through telephone after 2 weeks of treatment. We checked whether they continued to take the drug and whether they reported any adverse effect of salbutamol. We then re-evaluated pain intensity and symptom improvement at the first visit after a month of salbutamol use. Pain scores of the patients were significantly decreased after 1 month of therapy, and percent of pain relief declared by the patients was high. All accompanying symptoms were improved, except for numbness in two patients. None of the patients complained of any side effect related to the drug during the period they used salbutamol. Table 2 shows the pre- and posttherapy pain scores, the initial and recovered symptoms of the patients, and the total duration of continuing therapy.

We tried to contact the patients while this report was being written. Four of the six patients responded to our calls. Three patients (cases 2, 4, and 5) were still using the drug for 10 months without reporting any side effect. These patients confirmed continuing pain relief and improved accompanying symptoms sustained to the same degree as the initial assessment after a month. The fourth patient (case 1) declared that although she had acceptable pain relief during treatment period, she stopped using the drug after 3 months on her own decision.

Discussion

Optimizing the functions of the adrenergic system may provide pain relief because a primary dysfunction of adrenergic signaling has been reported in some, but not all, chronic pain conditions. Clinical studies have proposed a beneficial role of β -AR antagonists for musculoskeletal pain management,^{5,6} because catechol-*O*-methyltransferase polymorphism influences pain perception and altered sympathetic nervous system activity can be observed in these patients.^{1,3,18} However, catechol-*O*-methyltransferase polymorphism was reported to be unrelated to individual susceptibility to neuropathic pain, suggesting that persistent muscular pain and neuropathic pain may imply different mechanisms.¹⁹

Neuropathic pain often manifests itself with sensory symptoms and signs such as allodynia, aching, tingling, numbness, burning, cramp-like pain, stabbing, and shock-like pain, and these severe symptoms can have a significant effect on the quality of life of the patients.^{20,21} However, every patient has a different presentation of neuropathic pain, and their responses to the medications that are recommended for the treatment of neuropathic pain may vary.^{21–23} Thus, these drugs provide adequate pain relief to 40–60% of the patients only.^{12,20} Mechanism-based approach for selection of neuropathic pain therapy may provide better pain relief.^{22,24} Thanks to animal models, there is major progress in understanding the mechanisms of the neuropathic pain and treatment modalities, and potential new targets for treatment have been identified.²⁵

Many drugs are available for neuropathic pain management; however, antidepressants remain a first-line treatment.^{12,23,26,27} These drugs primarily act on aminergic reuptake sites.²⁶ Recent animal studies revealed that the noradrenaline recruited by antidepressants act through β_2 -ARs to relieve neuropathic allodynia.^{13,14} Indeed, the antiallodynic action of antidepressants is blocked by coadministration of a β_2 -AR antagonist and is absent in β_2 -AR-deficient mice.^{13,14} Furthermore, pre-clinical studies have reported that a direct stimulation of β_2 -ARs can be sufficient to alleviate neuropathic allodynia.^{15–17} Indeed, β -mimetics such as bambuterol, clenbuterol, fenoterol, formoterol, isoprenaline, metaproterenol, procaterol, terbutaline, ritodrine, salbutamol, or salmeterol were shown to provide allodynia relief after chronic treatment in a murine model of neuropathic pain.^{15–17} This action was reported to be similar to antidepressants.

In the current case report, the common feature of the patients was their resistance to previous therapeutic approaches for neuropathic pain and symptom management. They were referred to the pain clinic with moderate to severe symptoms and inadequate pain relief with ceased or ongoing therapies. They had no contraindication for the use of any β_2 -AR agonist agent.

Because β_2 -AR agonist agents are readily available and widely used drugs in medicine, they have well-described fea-

Table 1. The Characteristics of the Patients and Background of Neuropathic Pain

Case No.	Age, yr	Gender	Weight, kg	Height, cm	Cause of the Neuropathic Pain	Referral to the Pain Clinic*	Previous Therapies
1	75	F	90	160	Lumbar radiculopathy	2 mo	TCA, NSAID, physical therapy
2	47	M	65	170	Traumatic	2 mo	TCA, NSAID
3	70	F	55	160	Lung cancer	2 mo	TCA, NSAID, pregabalin, fentanyl patch, tramadol
4	60	M	70	160	Traumatic	1 yr	TCA, NSAID, gabapentin steroid
5	44	M	80	165	Lumbar spinal stenosis	1 yr	TCA, myorelaxants, acupuncture
6	57	M	60	170	Lung cancer	2.5 yr	TCA, NSAID, fentanyl patch, tramadol

* Delay between first visit at our pain clinic and the start of salbutamol treatment.

NSAID = nonsteroidal antiinflammatory drugs; TCA = tricyclic antidepressants.

Table 2. Pre- and Posttherapy Visual Analog Pain Scores, Initial and Recovered Symptoms, and Duration of Therapy

Case No.	Pretherapy VAS	Posttherapy VAS	Decrease in VAS Declared by Patient, %	Initial Symptoms	Unimproved Symptoms	Side Effects	Total Duration of Therapy, mo
1	8	0	99	Aching, allodynia, tingling, numbness	None	None	7
2	9	4	50	Pain, allodynia, burning sensation, numbness	None	None	5
3	6	0	90	Aching, allodynia, tingling, numbness	Numbness	None	5
4	10	5	50	Pain, allodynia, stabbing, numbness	None	None	1
5	10	4	60	Stabbing pain, cramp-like pain, allodynia, burning sensation, numbness	Numbness	None	2
6	10	3	75	Stabbing and shock-like pain, allodynia, numbness	None	None	3.5

VAS = Visual Analog Pain Scale.

tures and adverse effects. Although both nonselective and selective β_2 -AR agonists suppressed allodynia after chronic treatment,^{15–17} we preferred to use a short-acting selective β_2 -AR agonist to limit the undesirable events at the very least. Thus, we chose salbutamol, also known as albuterol in the United States, in a slow-release form to increase compliance of the patients and to limit potential side effects. The use of a nonselective agonist would have more systemic side effects, and possible adverse events initiated by a long-acting agent would have persisted longer.

All patients achieved significant symptom relief, especially in pain, after salbutamol use for a month. Other neuropathic symptoms were also improved. Interestingly, we observed a relief of allodynia, which is usually considered as an extremely treatment-resistant symptom in neuropathic pain. Potential adverse effects associated with the use of salbutamol may include fine tremor, dry mouth, nervousness, headache, muscle cramps, tachycardia, arrhythmias, and sweating. None of the six patients reported these adverse events at the dose used in this study. This lack of adverse events and satisfaction with the treatment provided patient compliance with the treatment.

Our findings proposing a beneficial action of a β_2 -AR agonist in neuropathic pain condition somehow seem to be contrary to the proposed beneficial role of β -AR antagonists in musculoskeletal pain conditions. However, various types of pain may indicate various underlying mechanisms and require different therapeutic approaches. Indeed, even for musculoskeletal pain, the study of β_2 -AR haplotypes suggested that either β_2 -AR hyperfunction (60–70% of patients) or hypofunction (25–30% of patients) may contribute to the pain condition.⁴ In this regard, patients with

β_2 -AR hypofunction should not respond to treatment with an antagonist.⁴ Tailoring the patients' management according to the different types of chronic pain and their underlying mechanism may thus be critical for successful management of chronic pain conditions.

In conclusion, we suggest that salbutamol may be an effective treatment option in patients with neuropathic pain resistant to commonly used therapeutics. However, one should prudently interpret the results, because the current findings were obtained without blinding, randomization, or a control group. This case report may encourage further randomized, controlled, prospective, and blinded studies to evaluate more thoroughly the use of β -mimetic agents as therapeutic alternatives for neuropathic pain.

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