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RECENT DRUGS FOR THE MANAGEMENT AND TREATMENT OF FIBROMYALGIA

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Abstract:

Fibromyalgia is a disorder, which is characterized by widespread musculoskeletal pain accompanied by fatigue, memory, mood, and sleep issues. Scientists believe that this condition may be due to injury, emotional distress, or viruses that change the way the brain perceives pain, but the exact cause is unclear. Generally, fibromyalgia is treated with antidepressants, pain relievers, and Anti-seizure drugs. There is not much specific treatment available for the treatment and management of fibromyalgia. Duloxetine hydrochloride (Cymbalta), milnacipran hydrochloride (Savella) and pregabalin (Lyrica) are the only drugs which have been officially approved by the US Food and Drug Administration for the management / treatment of fibromyalgia. Milnacipran hydrochloride is the first drug introduced primarily for treating fibromyalgia. Some drugs are also in the pipeline for the treatment and management of fibromyalgia, for example, Tuscaloosa is developing IMC-1, Theravance is developing TD-9855, Astella is developing ASP8062 and ASP0819. Researchers are also looking to explore new therapeutic targets with respect to Substance P and other neurotransmitters, which are implicated in the pathogenesis of fibromyalgia. It would be interesting to note the outcomes related to the development of new drugs for the treatment and management of fibromyalgia.

Keywords: *Fibromyalgia, Duloxetine, Milnacipran, Pregabalin, Pipeline drugs.*

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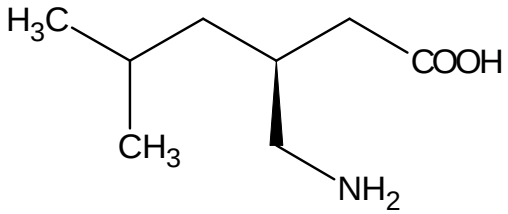
INTRODUCTION:

Fibromyalgia is an idiopathic condition of widespread musculoskeletal pain that is characterized by pain, soft tissue tenderness, general fatigue, stiffness and sleep disturbances as well as cognitive dysfunction [1-2]. Although, it is one of the most common diseases affecting the muscles leading to chronic pain and disability, its cause is currently not clearly defined. However, it is supposed to be linked to several changes in brain neurotransmitters, particularly serotonin and norepinephrine [3-5]. This disease is estimated to affect about 2% to 8% of the adult population worldwide and is considered to be the common cause of generalized, musculoskeletal pain in women between the ages of about 20 years to 55 years [6-8]. There are no blood tests or X-ray tests that specifically point the doctor to the diagnosis of fibromyalgia. The tests are done to exclude other possible diagnoses. Therefore, the diagnosis of fibromyalgia is made purely on clinical grounds based on the doctor's history and physical examination [9-11]. Traditionally, the most effective medications in the treatment of fibromyalgia have been the tricyclic antidepressants, for example, amitriptyline and doxepin [12,13]. There is not much specific treatment available for the treatment and management of fibromyalgia. Duloxetine hydrochloride, milnacipran hydrochloride and pregabalin are the only drugs which have been officially approved by the US Food and Drug Administration for the management / treatment of fibromyalgia.

Pregabalin (Lyrica)

Pregabalin was approved by the US Food and Drug Administration for the management of fibromyalgia in June 2007. It was the first drug to be approved for this indication and was sponsored by Pfizer. Pregabalin is a 3-substituted analogue of GABA that binds selectively to the alpha$_2$-delta subunit of the voltage-gated calcium channel. Its exact mechanism of action is not known, but may be due to the reduction in the release of several neurotransmitters resulting in analgesic, anticonvulsant, and anxiolytic effects. Chemically, pregabalin is (S)-3-(aminomethyl)-5-methylhexanoic acid [14-16].



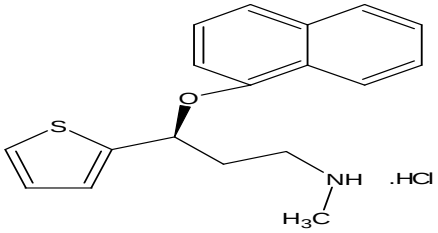
Chemical structure of pregabalin

Pregabalin is a white to off-white, crystalline solid with a pKa1 of 4.2 and a pKa2 of 10.6. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05 M phosphate buffer) at pH 7.4 is -1.35. It is available as capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg of pregabalin for oral administration. It is also available as solution, 20 mg/mL, for oral administration [17-19].

Pregabalin was previously approved by the US Food and Drug Administration to treat seizures, as well as pain from damaged nerves that can happen in people with diabetes (diabetic peripheral neuropathy) and in those who develop pain following the rash of shingles. Side effects of Lyrica, including sleepiness, dizziness, blurry vision, weight gain, trouble concentrating, swelling of the hands and feet, and dry mouth. Allergic reactions, although rare, can occur [17-19].

Duloxetine hydrochloride (Cymbalta)

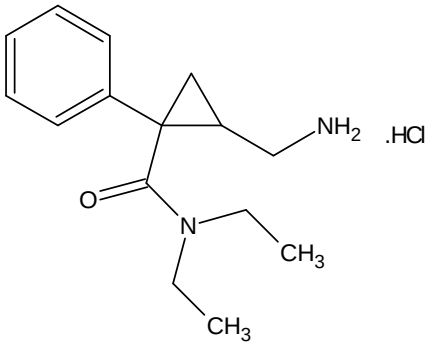
Duloxetine hydrochloride was approved by the US Food and Drug Administration for the management of fibromyalgia in June 2008. Duloxetine hydrochloride is a potent serotonin-norepinephrine reuptake inhibitor (SNRI) and a less potent inhibitor of dopamine reuptake. The exact mechanism of action is unknown, but it is believed that its effects on depression, anxiety, and pain perception may be due to increased activity of serotonin and norepinephrine in the CNS. Chemically, duloxetine hydrochloride is (+)-(S)-N-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride [20-22].



Chemical structure of duloxetine hydrochloride

The empirical formula is $C_{18}H_{19}NOS.HCl$, which corresponds to a molecular weight of 333.88. Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water. Duloxetine hydrochloride is marketed as capsule containing enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach [23-25].
Cymbalta, marketed by Eli Lilly and Co., was previously approved by the US Food and Drug Administration to treat depression, anxiety, and diabetic peripheral neuropathy. Cymbalta's side effects include nausea, dry mouth, sleepiness, constipation, decreased appetite, and increased sweating. Like some other antidepressants, Cymbalta may increase the risk of suicidal thinking and behavior in people who take the drug for depression. Some people with fibromyalgia also experience depression [23-25].

Milnacipran hydrochloride (Savella)
Milnacipran hydrochloride was approved by the US Food and Drug Administration for the treatment of fibromyalgia in January 2009. Milnacipran hydrochloride is a selective norepinephrine and serotonin reuptake inhibitor; it inhibits norepinephrine uptake with greater potency than serotonin. It is a racemic mixture with the chemical name: (±)-[1R(S),2S(R)]-2-(aminomethyl)-N,N-diethyl-1-phenylcyclopropanecarboxamide hydrochloride [26-28].



Chemical structure of milnacipran hydrochloride

It has been used since 1997 in parts of Europe and Asia for the treatment of depression. Currently, its only indication in the U.S.A. is for the management of fibromyalgia. The sponsor of milnacipran hydrochloride is Forest Laboratories. Milnacipran hydrochloride is a white to off-white crystalline powder with a melting point of 179°C. It is freely soluble in water, methanol, ethanol, chloroform, and methylene chloride and sparingly soluble in diethyl ether. It has an empirical formula of $C_{15}H_{23}ClN_2O$ and a molecular weight of 282.8 g/mol. Savella is available for oral administration as film-coated tablets containing 12.5 mg, 25 mg, 50 mg, and 100 mg milnacipran hydrochloride [26-28].
Savella, marketed by the Forest Pharmaceuticals, Inc., is the first drug introduced primarily for treating fibromyalgia. Savella is not used to treat depression in the United States, but acts like medicines that are used to treat depression (antidepressants) and other mental disorders. Side effects of milnacipran hydrochloride include nausea, constipation, dizziness, insomnia, excessive sweating, vomiting, palpitations or increased heart rate, dry mouth and high blood pressure [29-31].

CONCLUSION:

There are only three specific FDA approved drugs for the management of fibromyalgia. Some drugs are under pipeline for the treatment and management of fibromyalgia. Recently, Tuscaloosa, Alabama-based Innovative Med Concepts, a biotech company has announced that it has been granted U.S. Food and Drug Administration Fast Track Designation for the development of IMC-1, which is the lead drug candidate in its pipeline for the treatment of fibromyalgia. Similarly, TD-9855, a novel norepinephrine and serotonin reuptake inhibitor is being developed by Theravance for the management of fibromyalgia. ASP8062, a $GABA_B$ receptor positive allosteric modulator is being developed by Astellas for the treatment and management of fibromyalgia. Astella is also developing ASP0819, a $Calcium^{2+}$activated K^+ channel opener for the same indication. According to the American College of Rheumatology (ACR), people with fibromyalgia can have abnormal levels of Substance P in their spinal fluid. This chemical helps transmit and amplify pain signals to and from the brain. Accordingly, researchers are also looking at the role of Substance P and other neurotransmitters, and studying why people with fibroyalgia have increased sensitivity to pain and whether there is a gene or genes that make a person more likely to have it. It would be interesting to note the outcomes related to the development of new drugs for the treatment and management of fibromyalgia.

REFERENCES:

1.Diers M, Koeppe C, Yilmaz P, Thieme K, Markela-Lerenc J, Schiltenwolf M, van Ackern K, Flor H. Pain ratings and somatosensory evoked responses to repetitive intramuscular and intracutaneous stimulation in fibromyalgia syndrome. J Clin Neurophysiol, 2008; 25(3):153-160.

2.Stahl SM. Fibromyalgia-pathways and neurotransmitters. Hum Psychopharmacol Clin Exp, 2009; 24 (suppl 1):S11-S17.

3.Perrot S, Dickenson AH, Bennett RM. Fibromyalgia: harmonizing science with clinical practice considerations. Pain Pract, 2008; 8:177-189.

4.Lyseng-Williamson KA, Siddiqui MA. Pregabalin: A review of its use in fibromyalgia. Drugs, 2008; 68:2205-2223.

5.Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. Neuroscience, 2016; 338:114-129.

6.Hauser W, Wolfe F. Diagnosis and diagnostic tests for fibromyalgia (syndrome). Reumatismo, 2012; 64(4):194-205.

7.Häuser W, Arnold B, Eich W, Felde E, Flügge C, Henningsen P, Herrmann M, Köllner V, Kühn E, Nutzinger D, Offenbächer M, Schiltenwolf M, Sommer C, Thieme K, Kopp I. Management of fibromyalgia syndrome--an interdisciplinary evidence-based guideline. Ger Med Sci, 2008; 6:Doc14.

8.Russell IJ, Larson AA. Neurophysiopathogenesis of fibromyalgia syndrome: a unified hypothesis. Rheum Dis Clin North Am, 2009; 35(2): 421-435.

9.Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB, Yunus MB. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken), 2010; 62(5): 600-610.

10.Moldofsky H. The significance of dysfunctions of the sleeping/waking brain to the pathogenesis and treatment of fibromyalgia syndrome. Rheum Dis Clin North Am, 2009; 35(2): 275-283.

11.Goldenberg DL. Multidisciplinary modalities in the treatment of fibromyalgia. J Clin Psychiatry, 2008; 69 Suppl. 2:30-34.

12.Hassett AL, Gevirtz RN. Nonpharmacologic treatment for fibromyalgia: patient education, cognitive-behavioral therapy, relaxation techniques, and complementary and alternative medicine. Rheum Dis Clin North Am, 2009; 35(2):393-407.

13.Arnold LM. Strategies for managing fibromyalgia. Am J Med, 2009; 122 (12 Suppl):S31-S43.

14.Parsons B, Argoff CE, Clair A, Emir B. Improvement in pain severity category in clinical trials of pregabalin. J Pain Res, 2016; 9:779-785.

15.Gerardi MC, Atzeni F, Batticciotto A, Di Franco M, Rizzi M, Sarzi-Puttini P. The safety of pregabalin in the treatment of fibromyalgia. Expert Opin Drug Saf, 2016; 11:1-8.

16.Derry S, Cording M, Wiffen PJ, Law S, Phillips T, Moore RA. Pregabalin for pain in fibromyalgia in adults. Cochrane Database Syst Rev, 2016; 9:CD011790.

17.Bhusal S, Diomampo S, Magrey MN. Clinical utility, safety, and efficacy of pregabalin in the treatment of fibromyalgia. Drug Healthc Patient Saf, 2016; 8:13-23.

18.Clair A, Emir B. The safety and efficacy of pregabalin for treating subjects with fibromyalgia and moderate or severe baseline widespread pain. Curr Med Res Opin, 2016; 32(3):601-609.

19.Lyseng-Williamson KA, Siddiqui MA. Pregabalin: a review of its use in fibromyalgia. Drugs, 2008; 68:2205-2223.

20.Häuser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain, 2010; 11(6):505-521.

21.Murakami M, Osada K, Mizuno H, Ochiai T, Alev L, Nishioka K. A randomized, double-blind, placebo-controlled phase III trial of duloxetine in Japanese fibromyalgia patients. Arth Res Ther, 2015; 17:224 DOI: 10.1186/s13075-015-0718-y.

22.Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev, 2014; (1):CD007115.

23.Curran MP. Duloxetine: in patients with fibromyalgia. Drugs, 2009; 69(9):1217-1227.

24.Wright CL, Mist SD, Ross RL, Jones KD. Duloxetine for the treatment of fibromyalgia. Expert Rev Clin Immunol, 2010; 6(5): 745-756.

25.Ursini F, Pipicelli G, Grembiale RD. Efficacy and safety of duloxetine in fibromyalgia. Clin Ter, 2010; 161(4): 391-395.

26.Cording M, Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for pain in fibromyalgia in adults. Cochrane Database Syst Rev, 2015; DOI: 10.1002/14651858.CD008244.pub3.

27.Derry S, Gill D, Phillips T, Moore RA. Milnacipran for neuropathic pain

and fibromyalgia in adults. Cochrane Database Syst Rev, 2012; (3):CD008244.
28.Chwieduk CM, McCormack PL. Milnacipran: in fibromyalgia. Drugs, 2010; 70(1): 99-108.
29.Kranzler JD, Gendreau RM. Role and rationale for the use of milnacipran in the management of fibromyalgia. Neuropsychiatr Dis Treat, 2010; 6: 197-208.
30.Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. Clin Ther, 2008; 30:1988-2004.
31.Mease PJ, Clauw DJ, Gendreau RM, Rao SG, Kranzler J, Chen W, Palmer RH. The efficacy and safety of milnacipran for treatment of fibromyalgia. A randomized, double-blind, placebo-controlled trial. J Rheumatol, 2009; 36:398-409.