

Duloxetine, a Multitarget Drug

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Abstract

This review presents an overview of the multi targets of the duloxetine drug which was a product of the famous Eli Lilly Company. Although there is little evidence that the studies reproduce, it is clear that different transmitters or receptor types are involved in hyperalgesia and chronic pain which duloxetine mainly targets. While most attention has been focused on neuro transmitters and serotonin-norepinephrine reuptake mechanisms proving the drug efficacy in most discussed aspects. It is mainly known to work by raising the quantity of natural substances, serotonin and norepinephrine in the brain that helps maintaining the mental balance and pause the movement of pain signals in the brain. Any how the side effects are never correlated with the misuse of the drug dosage.

Keywords: Duloxetine; Neuro transmitters; Drug multitarget

Introduction

Eli Lilly and Company, a global pharmaceutical company which has the history of Mass producing Penicillin for the first time is also the host for marketing the pharma product Duloxetine with commercial brand names Cymbalta, Ariclaime, Xeristar, Yentreve, Duzela. It is a serotonin norepinephrine reuptake inhibitor which was basically effective for major depressive disorder and generalized anxiety disorder. But various researches made upon this drug showed the efficacy of the drug to be a Multi Target. This review mainly focused to cover few of the major targets like Major depressive disorder, Stress urinary incontinence, Diabetic peripheral neuropathy, Generalized anxiety disorder, Fibromyalgia, Chronic fatigue syndrome, Interstitial cystitis, Musculoskeletal pain. In this review I tried to show the various research impacts of Duloxetine Drug efficacy in colossal pathological targets (Figure 1). The pharmacology includes blocking the reuptake of serotonin and noradrenalin within the central nervous system. Major depressive disorder includes increase in pro-inflammatory cytokines within the central nervous system. Antidepressants cause a decrease in proinflammatory cytokine activity and an increase in anti-inflammatory cytokines; this mechanism is applicable to duloxetine in its effect on depression but research on cytokines specific to duloxetine therapy is still uncovered. The target of the drug in diabetic neuropathy and central pain syndromes such as fibromyalgia are believed to be due to sodium ion channel blockade. Duloxetine has no known significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors, but has an extensive metabolism. Elimination half life period of duloxetine is about 12 days with a steady state which is usually achieved after 3 days. Hepatic metabolism usually eliminates Duloxetine which involves two P450 isozymes, CYP2D6 and CYP1A2. The average absorption begins after 6 hours with maximum plasma concentrations.

Stress Urinary Incontinence (SUI)

Stress Urinary Incontinence (SUI) is most routinely found in women with stress. The major cause for this might be due to the weakening up of the sphincter pelvic muscle that supports the bladder and urethra. Antimuscarinic, adrenergic or anticholinergic drugs block bladder contractions which might help like anti-cholinergic drugs to control overactive bladder, Anti muscarinic drugs to block bladder contractions and Alpha-adrenergic agonist drugs to increase sphincter strength. Thus researchers basing these basic factors have carried out study using Duloxetine during routine clinical care in women with

stress urinary incontinence (SUI) in Germany, and in particular, to identify previously unrecognized safety issues as uncommon adverse reactions, and the influence of confounding factors present in clinical practice on the safety profile of duloxetine.

Disposable screen-printed sensors have been designed for determination of Duloxetine Hydrochloride [1]. Women newly started treatment for moderate to severe symptoms of SUI; 6,854 patients from urologist/gynecologist practices and 5879 primary care patients were reported in the observational study carried out by Michael MC et al. with parallel 12- week or 24- week administration of duloxetine which showed 15.9% (95% CI 14.9-16.9%) and 9.1% (CI 8.2-10.0%) in the 12- and 24-week treatment groups, respectively where 24 week study showed a positive screen for depressive disorder which was surprisingly common, but no case of suicide attempt was reported in either study [2].

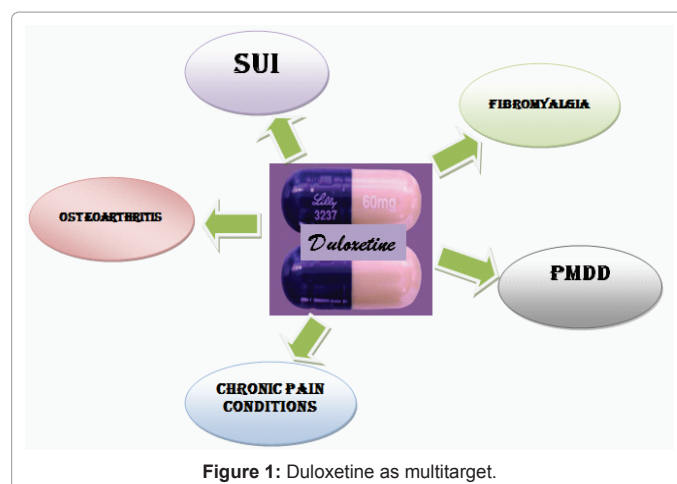


Figure 1: Duloxetine as multitarget.

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Gateway to Fibromyalgia

Fibromyalgia is rather a syndrome than a disease which causes widespread muscle pain and adds tenderness to joints. Fibromyalgia, a central nervous system disorder, is described as a 'central sensitization syndrome'. Studies that employed single-voxel magnetic resonance spectroscopy (1H-MRS) reported metabolic abnormalities within the hippocampal complex in patients with fibromyalgia. The "dopamine hypothesis of fibromyalgia" is connected to central abnormality responsible for symptoms associated with fibromyalgia which might be due to disruption of normal dopamine-related neurotransmission. In 1975, researchers hypothesized that serotonin regulates sleep patterns, mood, concentration and pain, could be involved in the pathophysiology of fibromyalgia-associated symptoms. In 1992, a study reports decreased serotonin metabolites in patient blood samples and cerebrospinal fluid. Studies with selective serotonin reuptake inhibitors (SSRIs) have met with limited success in alleviating the symptoms of the disorder, while drugs with activity as mixed serotonin-norepinephrine reuptake inhibitors (SNRIs) have been more successful which started to be a possible gateway. Recently examination of the predictors of adherence and persistence with duloxetine therapy in commercially insured FM patients was carried out by Zhanglin Cui & coworkers. Their study analyzed medical and pharmacy records over 1 year for patients in the US aged 18–64 years with FM who initiated (no prior 90-day use) duloxetine treatment in 2008. Medication possession ratio (MPR) was used to measure the Adherence to Duloxetine. High adherence was indicated as $MPR \geq 0.8$. Patients with high adherence and persistence with duloxetine were significantly older and had prior antidepressant use [3].

Premenstrual Dysphoric Disorder

Premenstrual dysphoric disorder (PMDD) is characterized by a range of physical and affective symptoms including anxiety, irritability, anhedonia, social withdrawal and depression. Premenstrual Dysphoric Disorder (PMDD) is a major hormonal brain-biochemistry problem that results in mood and behavioral distress. The symptoms originate mainly from two areas in the brain: the limbic area and up to the cortex. Different chemicals connect the limbic and cortex area of the brain: these are serotonin, dopamine, acetylcholine, and norepinephrine. Any changes in these chemicals affect a woman's mood and daily functioning. The limbic area is known to carry out various functions like memory, appetite, sleep, and strong emotions such as rage, anger, and aggression. The cortex area affects a person's judgment, attention, concentration, moods, perceptions, views, and interpretations of what is happening to them and around them. The latest research indicates that serotonin dysregulation is involved in PMDD. Women with severe PMDD symptoms can be treated with serotonin-reuptake inhibitors or SSRIs. When serotonin medications cannot be tolerated, a different type of antidepressant is an alternative. It enhances serotonin levels and balances the norepinephrine pathways. Li Y and co demonstrated robust and reproducible depression-like behavior during premenstrual protocols with various methodological variables. Forced swim test was used as evident with different routes of administration with and without exogenous estrogens in addition to progesterone, and in both single and multiple withdrawal paradigms. Progesterone withdrawal did not alter serotonin levels in the cortex or hippocampus. Furthermore tryptophan depletion did not augment immobility during PWD. In contrast, the tricyclic antidepressant was effective in reducing the immobility in forced swim test. These data demonstrate that progesterone withdrawal is a reproducible model of PMDD in several

critical behavioral domains and the data do not support alterations in serotonin levels in the etiology of hormonally induced depression [4].

Affectivity of the Drug in Models

Rat models were mostly used in the pre clinical study of duloxetine. The effects of acute systemic administration of various drugs like duloxetine, amitriptyline, mirtazapine and fluoxetine were compared in experimental models of gastric ulcer in rats in comparison with the vehicle control group. These results of that study carried out by Ji CX & coworkers highlighted the relationship in correlating antiulcer effect of drugs from different antidepressant classes across various animal gastric ulcer differently affecting both norepinephrine and serotonin levels which had more potent and efficacious antiulcer effect in various gastric ulcer rat animal models than drugs that only affected serotonin level (such as fluoxetine) [5].

Chronic Pain Conditions

A pain message is transmitted to the central nervous system (CNS) by special peripheral nervous system (PNS) nerve cells called nociceptors, which are distributed throughout the body and respond to different stimuli when neurotransmitters are released within the cell that facilitate nerve cell communication. Chronic pain is within the province of the peripheral nervous system, and the changeover occurs as the body attempts to adapt to the pain where the time limit used to define chronic pain typically ranges from three to six months, although some health care professionals prefer a more flexible definition, and consider chronic pain as pain that endures beyond a normal healing time. A study "*Efficacy of Duloxetine in Patients with Chronic Pain Conditions*" reviewed the efficacy of duloxetine in treating chronic pain using the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for clinical significance across chronic pain states which included pain intensity, patient ratings of overall improvement, physical functioning, and mental functioning. Average pain reduction was assessed over 3 months as the primary efficacy outcome. The analyses reported that duloxetine is efficacious in treating chronic pain as demonstrated by significant improvement in pain intensity, physical functioning, and patient ratings of overall improvement [6]. Although the antidepressant efficacy of duloxetine was not confirmed by the primary outcome, several secondary measures at multiple time points suggested efficacy. Duloxetine had significant and meaningful beneficial effects on pain & acute hepatic failure [7,8].

Efficacy in Chronic Musculoskeletal Pain

Chronic musculoskeletal pain is among the most frequent painful complaints that healthcare providers address. The bulk of these complaints are chronic low back pain and chronic osteoarthritis. Osteoarthritis results from articular cartilage failure induced by a complex interplay of genetic, metabolic, biochemical, and biomechanical factors with secondary components of inflammation. Osteoarthritis is the most common form of arthritis in the United States. Osteoarthritis and chronic low back pain may involve both nonpharmacologic (e.g., weight loss, resistive and aerobic exercise, patient education, cognitive behavioral therapy) and pharmacologic approaches. Analgesics are the first line medication for OA. The pharmacologic approaches to painful osteoarthritis remain controversial, but may include topical as well as oral nonsteroidal anti-inflammatory drugs, acetaminophen, duloxetine, and opioids. The role of duloxetine for musculoskeletal conditions is still evolving [9]. Pain is the leading symptom of osteoarthritis (OA) and is often chronic in nature, leading to significant morbidity and decreased quality of life. Duloxetine, a selective

serotonin norepinephrine reuptake inhibitor has been demonstrated to have a centrally acting analgesic effect [10,11] as it directly links back targeting to the inflammatory pathway. Study findings by Abou-Raya S et al. provide evidence for the efficacy and tolerability of duloxetine in reducing pain and subsequently improving function in older adults with knee OA [12]. Open-label duloxetine of a composite risk score (based on SLC6A2 rs5569 [G1287A] AA, HTR1A rs6295 [C(-1019)G] GG, and COMT rs174697 AA/AG) with 17-item Hamilton Depression Rating Scale total score change from baseline to 12 weeks was observed [13].

Tolerability of the Dosage

In accordance with standard teaching the drug is first evaluated for its safety and tolerability. At all stages of clinical development, the investigation includes safety, tolerability, pharmacokinetics, duration of action, efficacy, reversibility, concentration, patient acceptability, and commercial viability at the planned time of launch. Similar safety and tolerability of duloxetine in the treatment of children and adolescents with somatoform disorder was been investigated. The pharmacological treatments with antidepressants, benzodiazepines, stimulants and mood stabilizers only produced brief and partial improvement. Treatment with duloxetine (30 and 60 mg/day, respectively) experienced a gradual improvement that was maintained at 7 and 14 months which concluded the Duloxetine may be effective and well tolerated in the treatment of adolescents with somatoform disorder [14,15]. Duloxetine is a selective dual neuronal serotonin (5-Hydroxytryptamine, 5-HT) and selective-serotonin norepinephrine reuptake inhibitor (SSNRI). In accordance with FDA prescribing guidance regarding safety and drug-drug interactions, duloxetine 60 mg once-daily dosing appears to be an effective option in the appropriate pain patient population [16]. Physicians may be guided by their clinical experience to carefully consider the individual benefit/risk ratio and treatment-emergent adverse event (TEAE) susceptibility when deciding to start treatment with Duloxetine [17].

Conclusion

In this review I tried to explain the major targets by Duloxetine, a multi target drug which was actually manufactured as an anti depressant. But any drug which has been known to show its own efficacy also has its own side effects based on the usage. So even I would like to conclude with the same that duloxetine though being a multi target it is known to show certain severe side effects like suicidality, discontinuation syndrome & as such based on the chronic usage with a high dosage.

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