

USE OF ANTIDEPRESSANTS IN OFF LABEL THERAPY

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Abstract

Currently, there has been an increase in the use of antidepressants for pharmacological correction of not only depression, but also for treatment of many other pathological conditions, which determines their use as off label use (use of drugs outside the instructions). The performed analysis of data from scientific publications on PubMed platform allowed establishing that the most commonly prescribed off label antidepressants are selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). Among the pathological conditions in which antidepressants are used as off label use drugs, the following prevail: neuropathic pain in patients who do not suffer from depression; fibromyalgia; migraine; insomnia; premature ejaculation; bulimia nervosa; hives; urinary incontinence; premenstrual discomfort and other pathological conditions. It has been established that in recent years the use of off label antidepressants for various diseases has increased. Analyzing the problem of using off label antidepressants, it should be noted that doctors are poorly aware of this problem and the data obtained on off label use of antidepressants needs systematization, study and rational utilization. For that, physicians must be aware of the latest data on the use of off label antidepressants published in journals with high innovation ratings.

Keywords: *antidepressants, off label use, use of drugs outside the instructions*

Antidepressant drugs are widely used to treat depression, but despite this, they are often prescribed to treat many other pathological conditions [1, 2, 3, 4]. The prescription of antidepressants has increased especially significantly in recent years in many countries, including Australia, the United Kingdom, Canada and the United States [5, 6, 7, 8, 9], and today the global market for these drugs is estimated at \$ 13 billion [10]. At the same time, in the USA, about 10%, and in Canada, about 30% of all antidepressants are prescribed off-label (outside the instructions), which indicates a large scale of off-label use of these drugs [11].

The term "off label use" in pharmacotherapy was given in 1997 by the US Food and Drug Administration (FDA). In modern world medical practice, all medicines must obtain permission from regulatory authorities (for example, the FDA in the USA, the Ministry of Health in Ukraine) so that doctors and patients can use them in accordance with the instruction. Authorization is provided if a drug is considered safe and effective for an approved indication (on label prescription). The instruction of the drug is a guide for doctors, pharmacists, as well as patients on how to use the drug. According to the WHO, half of all drugs are prescribed for indications that are not in the instructions [12]. The concept of "use of drugs outside the instruction" - off label use has a wide meaning: use as indicated, in the patient population, in the dosage form, dose, regimen and route of administration, intelligence about does not contain which the approved drug instructions. Consequently, the off label drug has not been formally approved by the regulatory authority and no clinical trials have been conducted for such use [13,14].

The most commonly prescribed off label antidepressants are selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) [14]. The off label prescription of antidepressants for the treatment of chronic pain has increased especially significantly, and today there is already sufficient evidence regarding their effectiveness in this pathology [1, 16] and even their pharmacoeconomic advantages [17, 18]. Thus, a randomized double-blind study of patients with neuropathic pain, not suffering from

depression, has proven their effectiveness. The results of this study showed that a decrease in neuropathic pain was observed in 73% of patients taking SSRIs or SNRIs [19].

Antidepressants such as tricyclic (TCA) and SNRIs are believed to modulate serotonin and noradrenergic neurotransmission, which is dysfunctional in patients with neuropathic pain [19, 20]. Consequently, these drugs by regulating the level of neurotransmitters serotonin and norepinephrine in the brain, affect the formation of pain. However, as a rule, much lower doses of antidepressants are required for pain relief than for the treatment of depression [14, 16]. Therefore, the magnitude of the risk and potential side effects of antidepressants differ between the two indications. In addition, the analgesic effect after the administration of antidepressants appears in a shorter time than their antidepressant effect. Among all antidepressants for pain, TCAs are effective even at the lowest doses in comparison with other representatives of this group.

As a result, in 2009 the FDA approved the first antidepressant for the treatment of pain - milnacipram (Savella) (reduces phantom limb pain) [21]. Also currently, duloxetine is widely used off label for chronic pain, although initially the drug was approved for the treatment of depression, but later it turned out that it is also good at reducing neuropathic pain associated with diabetic peripheral neuropathy [22]. The situation with duloxetine is an example of how a drug from an applied off-label drug became an on-label drug. Numerous studies have demonstrated the effectiveness of duloxetine in the treatment of pain associated with knee arthritis, as well as neuropathic pain associated with diabetes, cancer and chemotherapy [23, 24]. Other results from a randomized, double-blind study support its efficacy in postoperative pain, resulting in decreased use of narcotic analgesics [25, 26].

Later, over the years, SSRIs and TCAs began to be used off label not only for chronic neuropathic pain, but also for the treatment of fibromyalgia [27, 28].

Chronic pain is often an integral part of rheumatoid arthritis (RA), but unfortunately there are currently no universal medications for the treatment of RA. RA therapy is primarily aimed at relieving pain and improving patients' ability to

move. Today, the antidepressant amitriptyline is recommended off label by rheumatologists for pain caused by RA [19, 24]. However, the mechanisms of the analgesic action of this drug are not fully understood. It is suggested that by affecting the content of neurotransmitters in the spinal cord, it reduces the transmission of pain impulses [24]. In addition, due to the blockade of voltage-gated sodium channels responsible for the generation of pain impulses, antidepressants to a certain extent reduce neuropathic pain [29]. Therefore, in clinical practice, antidepressants such as amitriptyline, duloxetine and citalopram are regularly used off label to treat chronic pain syndrome [1].

Migraine is one of the three most common diseases in the world and is the seventh pathology in terms of the importance of reducing the quality of life [30, 31]. It should be noted that antidepressants are used off label for the prevention of migraine, although they are not the first preventive and therapeutic aid for patients with migraine, however, their effectiveness in migraine has been clinically proven [32]. In particular, high doses of flunarizine are effective as a prophylactic agent for headaches [33].

Antidepressants make up a large number of off label drugs prescribed for the treatment of insomnia, which affects 40-50% of the world's population [34]. In the United States, 30% of men and 40% of women suffer from insomnia, and 21% of all prescribed antidepressants are used off label for insomnia. For example, in 2006 in the United States for insomnia, antidepressants were prescribed off label for an average of 45% of patients [35]. Symptoms of depression are common in chronic insomnia, and conversely, chronic insomnia itself can lead to depression. Therefore, despite the availability of a wide range of sleeping pills, antidepressants are used among popular drugs for the treatment of insomnia, especially after the antidepressant doxepin received FDA approval for this indication [36]. Ultra-low doses of this drug improve both the act of falling asleep and the duration of sleep. Low doses of trazodone are effective for the treatment of primary and secondary insomnia, while mirtazapine is administered for insomnia at doses similar to those used for the treatment of depression [34, 37].

To improve the process of falling asleep and the quality of sleep, pediatricians are even more likely to prescribe antidepressants for this purpose than psychiatrists [38]. Therefore, when sleep problems are due to anxiety or depression, then off label doxepin, mirtazapine and trazodone are prescribed in low doses, which can effectively treat the symptoms of mood disorders and associated insomnia. This current situation requires the development of a therapeutic strategy justifying the clinical use of off label antidepressants for insomnia.

Insomnia is not the only sleep disorder treated with antidepressants. Thus, sleep disturbance in the form of a temporary inability to move and speak upon awakening can be completely eliminated by clomipramine, which is recommended off label, especially in cases of severe sleep disturbances [39].

Premature ejaculation is the most common sexual disorder in men after 40 years of age (occurs in 30-70%) and is considered mainly not a pathophysiological, but a psychological problem, since men with such a disorder may suffer from depression or anxiety [40]. Therefore, the use of antidepressants (paroxetine, sertraline and fluoxetine), on the one hand, is indicated for the treatment of depression (at the same time the drugs are used on label), and on the other hand, for the prevention of premature ejaculation, when the same drugs are used as off label [40, 41]. Premature ejaculation is eliminated by the side effect of these SSRIs, which is to extend the time it takes to ejaculate. Effective off label therapy for premature ejaculation is not only paroxetine, sertraline, fluoxetine, but also escitalopram and clomipramine [40]. There is clinical evidence for the off label use of citalopram and paroxetine to reduce hot flashes during menopause, and SSRI antidepressants to relieve symptoms of premenstrual disorders, and TCAs to reduce symptoms of attention deficit hyperactivity disorder [42].

Diagnoses of anorexia nervosa, bulimia nervosa and other eating disorders negatively affect the physical and mental health of patients [43]. This pathology has the highest mortality rate of all mental health disorders. Today, promising positive results have been obtained for sertraline, imipramine, escitalopram, bupropion, duloxetine in eating disorders (bulimia nervosa) [44]. However, lisdexamphetamine, a prodrug of D-amphetamine, is

the only FDA-approved drug for this condition and is generally preferred over other antidepressants [45].

Consequently, the use of off label antidepressants is clinically effective for bulimia nervosa, but they are not formally approved for this therapeutic use. Despite this, off label citalopram and sertraline are now used in the pharmacotherapy of anorexia nervosa, bulimia nervosa and other eating disorders and binge eating disorders as an alternative treatment to restore normal nutrition [46]. The effectiveness of these drugs in eating disorders is associated with their influence on the activity of serotonin, norepinephrine and dopamine, which are involved in the pathogenesis of bulimia nervosa and other disorders of overeating [44].

Nicotine is recognized among the 4000 chemical compounds of tobacco as a substance that causes addiction to smoking. Marketing research has shown that nicotine addiction is more common in people with mental anxiety disorders: anorexia nervosa, schizophrenia, depression [46]. The atypical antidepressant bupropion has shown anti-nicotine activity and has therefore been approved by the FDA as a means for smoking cessation [47]. It is assumed that the antinicotine mechanism of action of bupropion is associated with the blockade of reuptake of neurotransmitters in synapses. However, SSRI antidepressants group are not effective in these cases, suggesting that is not alone serotonin in playing a role in nicotine addiction. Further research is needed in the future to establish which antidepressant groups may be effective to terminate smoking.

Also, antidepressants are used off label for urticaria (doxepin), urinary incontinence (amitriptyline, duloxetine, imipramine), for premenstrual discomfort (fluoxetine, sertraline, citalopram, paroxetine) [1, 28, 48, 49, 50, 51, 52].

CONCLUSIONS

Thus, as can be seen from this literature review, the use of off label antidepressants in various diseases has increased in recent years. This is due to the fact that depression often accompanies many types of pathologies, therefore, in these cases, antidepressants can not only eliminate it as a symptom of the disease, but at the same time affect the main causes and links of pathogenesis. Analysis

of a large number of clinical off label prescriptions of antidepressant drugs suggests that they may play a symptomatic and pathogenetic role in the pharmacotherapy of many diseases. However, taking into account the side effects of antidepressants (addiction to them, the risk of overdose), this should always be taken into account when prescribing them as off label therapy.

Analyzing the problem of using off label antidepressants, it should be noted that doctors are poorly aware of this problem and it is necessary to systematize, study and rationalize the data obtained on the off label use of antidepressants.

Currently, WHO and the FDA believe that the situation of effective off label drug use can be improved thanks to messages therapeutic experiences their application off label. Also, the use of off label antidepressants must necessarily be based on sound scientific evidence in the form of scientific articles or scientific conference discussions with a high degree of clinical evidence. To do this, physicians must be aware of the latest data on the use of off label antidepressants published in journals with high innovation ratings.

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