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THE OFF-LABEL USE OF DRUGS IN PSYCHIATRY

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Abstract

Antipsychotic drugs have revolutionized the treatment of mental diseases. Although these drugs are more commonly used to treat schizophrenia, they are also prescribed to treat many other conditions, including bipolar disorder, depression, personality disorders, dementia, and autism. During the Covid-19 pandemic, antiviral activity was found to be characteristic of some psychotropic drugs. Recently, it has become common to prescribe antipsychotic drugs for diseases that are not in the instructions (off label), since clinical trials for them are more complex than for other medicines. Most often, off-label drugs in psychiatry are used for unapproved indications and in doses that are not indicated in the current instructions for medical use. One of the main reasons for prescribing psychotropic drugs off-label is the need to treat patients who do not respond to traditional psychotherapy, i.e. resistant to it. Specialized literature indicates that the percentage of the frequency of off-label drugs prescriptions in psychiatry in terms of pharmacological groups is as follows: anxiolytics - 65%, antipsychotic drugs - 69%, antidepressants - 92%, antiepileptic drugs - 51%, stimulants of the central nervous system (CNS) - 30 %. Medicines most commonly prescribed off-label are risperidone (12%) [23], clobazam (12%), amitriptyline (11%), hydroxyzine (10%), diazepam (7%), clonazepam (12.4%), lorazepam (12%) and trihexyphenidyl hydrochloride (10%). Almost half (47%) of all off-label prescriptions were associated with symptoms such as anxiety (24%), behavioral disturbances (12%), and pain (11%)

Thus, analyzing the problem of the off-label use of drugs in psychiatry, we can conclude that the insufficient number or absence of clinical large-scale comparative evidence for the off-label use of antipsychotic drugs, the insufficient validity of these data, and the poor awareness of doctors in the search for information on this problem makes it difficult to determine the credibility of effectiveness and the safety of such use.

Keywords: *psychiatry, off-label use, depressive disorder, bipolar disorder, schizophrenia, obsessive-compulsive disorder, mania.)*

Antipsychotic drugs have revolutionized the treatment of mental diseases [42, 15, 10]. Although these drugs are more commonly used to treat schizophrenia, they are also prescribed to treat many other conditions, including bipolar disorder, depression, personality disorders, dementia, and autism [40, 41]. During the Covid-19 pandemic, antiviral activity was found to be characteristic of some psychotropic drugs [14]. Recently, it has become common to prescribe antipsychotic drugs for diseases that are not in the instructions (off label), since clinical trials for them are more complex than for other medicines [51, 6, 32].

According to many psychiatrists, including the American Psychiatric Association, physicians can prescribe drugs off label if the use is safe and effective in the professional judgment of the prescribing physician and if there is a documented clinical evidence of this [53, 12]. Although psychiatrists do not allow frivolous medical records, off-label prescribing nevertheless requires scrupulous recording of their use and preservation, including patient's informed consent [39]. However, a retrospective analysis of psychiatric prescriptions for some off-label drugs has confirmed the credibility of scientific evidence in only 4% of cases [47, 18].

One of the main reasons for prescribing psychotropic drugs off-label is the need to treat patients who do not respond to traditional psychotherapy, i.e. resistant to it. Some psychiatrists believe that off-label drug approval is not required because they are approved drugs but are used for other indications, especially since about 30% of diagnoses in psychiatry have a limited range of approved drugs for their treatment. Other practitioners believe that sometimes clinical trials in psychiatry do not include the majority of patients who are not followed up because of the severity of the disease, which is the reason for the off-label prescription [22]. However, the doctor is solely responsible for the off-label prescription, regardless of the reasons and the results achieved. Therefore, psychiatrists must be able to justify off-label prescriptions to use them in conjunction with standard psychotropic drugs in a real clinical setting. However, it should be noted that over the past two decades, the number of clinical trials of psychiatric drugs has increased due to the search for new indications for already approved psychotropic drugs [31]. In addition, changing indications for drugs used in psychiatry is common because the choice of approved psychotropic drugs is relatively limited. However, when a drug is effective, most psychiatrists are reluctant to change treatment [46, 16].

Most often, off-label drugs in psychiatry are used for unapproved indications and in doses that are not indicated in the current instructions for medical use. Thus, common diagnoses in psychiatry when drugs are prescribed off-label are depressive disorder (40.4%), bipolar disorder (26.8%), schizophrenia (20%), obsessive-compulsive disorder (2.8%), and mania (2%) [36]. A retrospective analysis [9, 52] has shown that for these indications, 980 off-label drugs (39.5%) were prescribed with an average amount per patient of 3.6 ± 1.42, and in 98% of patients, more than one off-label psychotropic drug was used. Diazepam (46.8%) was the most frequently prescribed off-label drug, followed by imipramine (22.8%) and lithium drugs (20.4%). High rates of psychotropic drugs off-label prescription were registered among children: the age group of adolescents (62%) leads, followed by younger children (37%) and newborns (1%) [50, 21]. Retrospective studies in the EU have shown that in 62% of pediatric outpatients off label drugs were prescribed by psychiatrists [36]. In the United States, more than one in five outpatient off-label psychotropic prescriptions occurs in children [55]. The largest proportion of off-label prescriptions in children occurs before the age of 6, but this is due to indications, not age. Consequently, psychotropic drugs are some of the most common off-label drugs, and their use in children is of particular concern, as clinical trials and approvals for psychotropic drugs in this age group are longer and less frequent [55].

Specialized literature indicates that the percentage of the frequency of off-label drugs prescriptions in psychiatry in terms of pharmacological groups is as follows: anxiolytics - 65%, antipsychotic drugs - 69%, antidepressants - 92%, antiepileptic drugs - 51%, stimulants of the central nervous system (CNS) - 30 %. Medicines most commonly prescribed off-label are risperidone (12%) [23], clobazam (12%), amitriptyline (11%), hydroxyzine (10%), diazepam (7%), clonazepam (12.4%), lorazepam

(12%) and trihexyphenidyl hydrochloride (10%). Almost half (47%) of all off-label prescriptions were associated with symptoms such as anxiety (24%), behavioral disturbances (12%), and pain (11%) [36].

An analysis of prescribing drugs in psychiatry showed more frequent use of off-label benzodiazepines compared to atypical antipsychotic drugs: off-label benzodiazepines were prescribed in 42.4%, atypical antipsychotic drugs - only in 5.6% of patients [2]. Psychiatrists prescribed benzodiazepines for insomnia and to relieve aggressive symptoms in schizophrenic patients. Clonazepam, lorazepam, and diazepam are more often used off-label for depression, mania, bipolar and obsessive-compulsive disorders to quickly relieve anxiety. Clonazepam has anti-anxiety and anticonvulsant effects in epilepsy [4]. With a low dose and long-term use, clonazepam exhibits a preventive effect of depression relapse, which has been used to treat persistent or prolonged depression, as well as to accelerate the onset of the effects of conventional antidepressants [45].

Off-label antidepressants are most commonly used in the United States, where about 10% of patients are taking these medicinal products. Antidepressants increase the levels of the neurotransmitters serotonin and norepinephrine in the brain, influencing the formation of pain. Therefore, SSRIs (selective serotonin reuptake inhibitors) and TCAs (tricyclic antidepressants) have been used off-label for chronic neuropathic pain and the treatment of fibromyalgia for many years [51]. In 2009, the US FDA had approved the first antidepressant for the treatment of fibromyalgia - milnacipran (Savella), and in 2010 - duloxetine (Simbalta) for treating not only depression but also fibromyalgia [36].

Clonazepam and gabapentin have been commonly prescribed off-label in psychiatry for the treatment of neuralgic headache, restless legs syndrome, nonspecific arthralgia, and sinus tachycardia. In 1993, the FDA approved Pfizer gabapentin under the trade name Neurontin only for the treatment of seizures. However, for many years this drug has been widely used off-label for the treatment of pain, mental disorders, migraines, insomnia, i.e. for indications that have not been approved by the FDA [49, 43].

Duloxetine was originally approved for the treatment of depression as a selective serotonin reuptake inhibitor (SSRI). However, it also appears to be good at reducing neuropathic pain associated with diabetic peripheral neuropathy. In 2005, the FDA approved duloxetine as a treatment for neuropathic pain. The situation with duloxetine is an example of how a drug from an off-label became an on-label [46].

In addition, SSRIs (eg, paroxetine, sertraline, and fluoxetine) are used off-label to treat premature ejaculation [5]. This condition is the most common sexual disorder in men in their 40s (30–70%) and is considered not a physical but a psychological problem. Men with this disorder may suffer from depression or anxiety. The use of antidepressants, on the one hand, is indicated for the treatment of depression in such patients, while the drug is used on-label, and on the other hand, to prevent premature ejaculation when the same medicine is used off-label [33]. Premature ejaculation is eliminated due to the side effect of SSRI drugs, which consists in prolonging the time required for its commission [36]. But perhaps the best (albeit controversial) example of age safety is adolescent suicidal behavior with antidepressant use.

This problem was first identified when GSK has decided to expand the use of paroxetine (SSRI) and use it in children with depression [27]. At the time (1999), this GSK drug was approved for the treatment of depression in adults. A report from a clinical study on paroxetine in a new population, submitted by the company to the regulatory authority, provided evidence of an increase in the number of suicidal thoughts/intentions among adolescents aged 12 to 18 years who received this drug [30, 13]. It should be noted that trials in adolescents showed not only an increase in suicidal thoughts but also no improvement in the terminal stages of depression. Unfortunately, the results of this study were misrepresented by GSK in an article published in a reputable scientific journal. The authors, most of whom knew almost nothing about the essence of the study, calling it "successful", buried the problem of suicidal thoughts called "emotional lability." Later, GSK successfully obtained regulatory approval for the use of paroxetine in adults for other conditions such as

post-traumatic stress disorder (PTSD), obsessive-compulsive disorder, anxiety, and panic disorder [5].

The problem of suicidal behavior is a complex issue. First, it appears that the greatest risk in this area with paroxetine is concentrated in children, adolescents, and young patients under 24 years of age. This problem is virtually non-existent and is at the placebo level among older people receiving paroxetine [44]. In the treatment of adults over 24 years of age, paroxetine is effective without an overall increased risk of suicidal behavior. At the same time, paroxetine in the treatment of children turned out to be an ineffective antidepressant with an increased risk of suicidal thoughts. Second, suicide and thoughts about it are common in depression. A 2007 study [44] has shown that suicide attempts are most often made one month before starting treatment. After initiation of any form of treatment, there is a marked decrease in this behavior. By the age of 25, specialized medical care, antidepressant pharmacotherapy, or psychotherapeutic counseling, reduces the likelihood of attempting suicide. The study showed a similar result in elderly patients [3].

These findings are supported by two pieces of evidence. The first is the study results published in the British Medical Journal in 2012, which reported that adolescent suicide attempts increased by 21.7% 2 years after the FDA warned about the risk of suicidality with antidepressant drugs, resulting in a 31 % decrease in the consumption of these medicines. At the same time, the number of suicidal thoughts among people aged 18 to 29 increased by 33.7%. The second piece of evidence is a study by a group of psychiatrists who, for the first time, evaluated individual data on individual subjects to review suicide and thoughts of suicide along with depression during the treatment period [30]. The general finding from the use of two SSRIs (fluoxetine and venlafaxine) is that these drugs do reduce depression and are more effective in older people than in younger people [51].

Children and adults with depression behave in completely different ways, and many antidepressants (not only from the SSRI group but also amitriptyline and imipramine) can cause increased suicidality in young people. A study conducted in Germany on the off-label use of drugs in children showed that in 17% of cases when prescribing a drug, doctors ignored recommendations regarding the active ingredient, dose, or specific age group [1].

Modafinil is approved by the FDA in the United States for the treatment of narcolepsy, sleep apnea, and sleep disturbances associated with work shifts change. But this drug is used off-label in the treatment of ADHD and myotonic dystrophy syndrome. Myotonic muscular dystrophy (MMD) syndrome is characterized by muscle weakness. Daytime sleepiness is often associated with MMD in patients experiencing muscle weakness with impaired breathing and swallowing. There is no specific treatment for MMD yet, and existing treatments are focused on correcting symptoms and minimizing disability. Treatment with modafinil for daytime sleepiness or fatigue is acceptable for use off-label in MMD [37].

In the United States, 30% of men and 40% of women suffer from insomnia. In 21% of all prescribed antidepressant prescriptions, they are used off-label for insomnia. For example, in 2006 in the United States for insomnia, antidepressants were prescribed off-label on average in 45.1% of patients. Pediatricians were more likely to prescribe off-label antidepressants for this purpose than psychiatrists. The current situation obliges to develop a strategy justifying the clinical off-label use of antidepressants for insomnia [51]. When sleep problems are due to anxiety or depression, low-dose off-label antidepressants, such as amitriptyline, mirtazapine, and trazodone, may be effective in treating symptoms of mood disorder and associated insomnia.

Abilify and other atypical antipsychotic drugs are used off-label to help patients fall asleep. Chronic insomnia in the case of delayed sleep phase syndrome associated with depression resolves after low-dose off-label treatment with this drug. However, with chronic insomnia, as a separate disease, the use of antipsychotics is inappropriate [7].

In 2009, the UK Department of Health published a report on the prescription of antipsychotic drugs for patients with dementia [19]. With rare exceptions, these drugs are not licensed in the UK for the treatment of the behavioral and mental symptoms of dementia. In the instructions for these drugs, as a rule, schizophrenia and bipolar disorders are

indicated. Therefore, the use of most antipsychotic drugs for dementia is off-label, except in those rare cases when a patient with dementia also has comorbid mental diseases[48, 56]. The report highlighted great concern about the inappropriate prescription of antipsychotic drugs to patients with dementia. The concern was that patients were not consulted before the initiation of such antipsychotic treatment, and it was not known whether or not they knew that their treatment was off-label [36].

Subsequently, the National Institute for Health and Care Excellence (NICE) has conducted its own assessment [35]. It was suggested that a quarter of patients (180,000) with dementia were prescribed antipsychotic drugs in addition to their usual treatment. The vast majority of them (8 out of 10) did not receive any benefit from antipsychotic therapy. Therefore, NICE opposed the use of any antipsychotic medication for dementia.

Moreover, these drugs turned out to be not only ineffective but also dangerous in elderly patients. There is an approximately threefold increased risk of developing cerebrovascular AR (strokes), which has been reported in randomized, placebo-controlled clinical trials in a population of patients with dementia who were taking some atypical antipsychotics, including risperidone, aripiprazole, and olanzapine [24]. As a result, NICE has calculated that out of every 100 patients who received atypical antipsychotic drugs for a year, one died prematurely, and the same number suffered from cerebrovascular complications such as stroke [34]. A similar situation was observed in the United States (2007), where social services found that over 6 months, 14% of nursing home patients received antipsychotic drugs and had similar adverse outcomes. In addition, when using antipsychotic drugs, excessive sedation is observed, which became the cause of falls or excessive inhibition of the central nervous system, when patients became "like zombies" [35].

Some antipsychotic drugs have been used off label to treat insomnia, anxiety, and aggressive behavior, as well as post-traumatic stress disorder (PTSD), although the evidence for their effectiveness in this area is weak (for example, risperidone has failed in clinical trials when used as an adjunct to PTSD symptom therapy) [25]. Therefore, compared to antidepressants, which are clearly effective in PTSD, antipsychotic drugs are a therapeutically extreme option. In addition to the nearly sevenfold increase in the off-label use of antipsychotic drugs, there has been an even greater increase in the off-label use of sedative anticonvulsants [54].

When pediatric and psychiatric drug use is analyzed, off-label prescriptions in child psychiatry are becoming even more common and issues of great concern are emerging. In the United States, this problem has been assessed by the American Medical Association regarding the fact that although some atypical antipsychotic drugs are FDA approved for specific conditions in pediatric practice, the majority (70–75%) are off-label [17].

One of the additional problems with atypical antipsychotic drugs is their adverse metabolic effects. Because the risk of childhood obesity is often linked to socioeconomic status, children from low-income families who already have a high risk of obesity and associated metabolic disorders may be particularly vulnerable to the effects of weight gain due to atypical antipsychotic drugs.

A significant part of pediatric psychotropic drugs is more often prescribed off-label to control aggressive behavior than to eliminate the root cause of the disease, which requires more expensive psychotherapeutic intervention [8, 11]. Some drugs are prescribed off-label to very young children. For example, children aged 1 and 2 years received off-label antipsychotic drugs for the treatment of autistic disorder and attention deficit hyperactivity disorder (ADHD) [38]. Therefore, the US Department of Health and social services have reviewed the use of antipsychotic drugs, including off-label, by Medicare beneficiaries under the age of 17, with an emphasis on drugs such as Seroquel (quetiapine), Zyprexa (olanzapine), Risperdal (risperidone) and Abilify (aripiprazole). Medicare spends more on antipsychotic drugs than on any other group of drugs, and there is evidence that 70% of the cost of these drugs in the US was paid by Medicare and other government programs [28].

Levothyroxine sodium (Synthroid) is a hormonal drug that is widely used in hypothyroidism. However, 48% of physicians believe that it is highly effective off-label in the treatment of depression in combination with antidepressants, especially in

cases of refractory depression. It has been proven that thyroid hormones affect mood, and in depression, they act as stimulants of antidepressants, which may be the reason for their use off-label.

According to official data presented in the specialized literature, generalized anxiety disorder (GAD) - excessive fear of everyday situations - occurs in almost 6.8 million adults, twice as often in women than in men. Patients with GAD experience difficulties with relaxation, concentration, easily get scared, get tired quickly, and experience headaches and muscle pains. GAD patients are usually treated with antidepressants, and in some cases with off-label antipsychotics, which can be used alone or in combination with antidepressants [20, 29]. However, the results of studies have demonstrated different activities of antipsychotic drugs in the treatment of generalized anxiety symptoms. Thus, quetiapine, when used off-label, was found to be more effective than a placebo in reducing the symptoms of generalized anxiety. It was also found that quetiapine reduces the risk of recurrence of the disease. However, ziprasidone, olanzapine, and risperidone have been ineffective in the treatment of GAD [26].

There is research showing that off-label use of citalopram may be beneficial in reducing aggressive and impulsive behavior and is superior to comparison drugs in the treatment of behavioral disorders associated with dementia.

Thus, analyzing the problem of the off-label use of drugs in psychiatry, we can conclude that the insufficient number or absence of clinical large-scale comparative evidence for the off-label use of antipsychotic drugs, the insufficient validity of these data, and the poor awareness of doctors in the search for information on this problem makes it difficult to determine the credibility of effectiveness and the safety of such use. However, the increasing off-label use of psychotropic drugs indicates the need to study this problem and the subsequent rational use of the data obtained.

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