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The use of buprenorphine in the treatment of drug-resistant depression – an overview of the studies

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Summary

There is evidence that the endogenous opioid system in the brain plays an important role in mood regulation, and disturbances in its functioning may lead to the occurrence of depressive disorders. One of the drugs that affect the endogenous opioid system in the CNS is buprenorphine. The article is a review of the studies on the effectiveness of buprenorphine used as an augmentation of antidepressant treatment. The selection of articles was made by browsing the Medline and PubMed databases with the use of key words 'buprenorphine' and 'treatment of drug-resistant depression'. The analysis included thirty one studies. The results indicate that buprenorphine may be effective in drug-resistant depression in a similar manner as other augmentation strategies added to antidepressant treatment. Co-administration of buprenorphine and samidorphan may reduce the risk of addiction without losing the antidepressant effectiveness of buprenorphine. Further methodologically correct studies in this field are needed. In addition to being a partial agonist of the μ receptor, buprenorphine is also a potent antagonist of the kappa type opioid receptors. The antagonism of μ receptors alone does not cause antidepressant effects. Antagonism towards kappa receptors may cause antidepressant effects as well as reduce the severity of anhedonia. Depressed patients who do not respond to standard antidepressant treatment may have dysfunctions of the kappa receptor that are similar to opioid addicts.

Key words: buprenorphine, depression, drug-resistant depression

Introduction

Depressive disorders are widespread and pose a significant public health problem. Epidemiological studies show that 21% of the US population and at least 15% of the world's population experience depression throughout life [1]. Depression significantly increases the risk of suicidal death. Depressive disorders affect the course of other chronic diseases, increasing morbidity and mortality [2, 3]. In the light of the results of the conducted studies, it has been revealed that standard methods of pharmacological

treatment of depression with the use of antidepressants have limited effectiveness [4, 5]. As noted by Zarate et al. [6], the development of new methods of treating drug-resistant depression is a significant problem. It is known that nearly 30% of patients do not respond to standard methods of treatment of depressive disorders [7]. 50–75% of patients in this population respond to electroconvulsive therapy, while 10–20% of patients do not respond to treatment [8].

Until the 1950s, opium was one of the primary methods of melancholia treatment [9]. The introduction of monoamine oxidase inhibitors and tricyclic antidepressants resulted in a significant reduction in the use of opiates in the treatment of depression. In recent years, there has been a growing interest in the influence of dysfunction of the opioid system on the formation of depressive disorders. There is evidence that the endogenous opioid system in the brain plays an important role in mood regulation [10], and disturbances in its functioning may lead to the occurrence of depressive disorders [11]. Agonism of the μ-type opioid receptors leads to the release of both serotonin and dopamine, which may cause an antidepressant action. The studies on the distribution of CNS receptors have shown that opioid receptors are densely distributed in the cortical and subcortical areas that are involved in the response to stress and integration of significant emotional signals [12]. By fully activating the μ-receptors, opioids have an analgesic and psychoactive effect.

One of the drugs that affect the endogenous opioid system in the CNS is buprenorphine. This drug's effectiveness in the treatment of pain is well-known. It exhibits partial agonism of the μ-type receptors, and is characterized by extremely high affinity and slow dissociation from opioid receptors [13]. This drug was approved by the US Department of Food and Drug Administration (FDA) in 2002 for the treatment of opioid addiction substitution. Buprenorphine has been shown to both reduce withdrawal symptoms and the risk of re-use of drugs.

Buprenorphine is a semi-synthetic derivative of thebaine, which is an opiate alkaloid. The drug binds stronger with the μ-type opioid receptor than morphine does but, simultaneously, it has lower intrinsic activity. This drug is well-soluble in fats and 96% of buprenorphine binds with plasma proteins. Due to low bioavailability after oral administration, what is a result of intestinal and hepatic inactivation, buprenorphine is best administered sublingually, intramuscularly and transdermally. The bioavailability of the drug varies from 55% to 90%. It penetrates the CNS well. The onset of action begins 5–10 minutes after intramuscular and 10–20 minutes after sublingual administration. Buprenorphine is metabolized by the liver to N-dealkylbuprenorphine (norbuprenorphine) and metabolites conjugated with glucuronic acid. The drug is excreted in feces (two-thirds, unchanged form) and urine (one-third, as metabolites). Buprenorphine's long duration of action can be accounted for its slow rate of dissociation from the opioid receptor. The registered indications for administering this drug in Poland are: relief of acute severe pain and chronic pain in the perioperative course as well as treatment of pain in myocardial infarction and during active cancer treatment (transdermal or sublingual route). The drug is also registered for opioid addiction (sublingual route) administered for the pharmacological, social and psychological treatment in adults. Contraindications

include significant respiratory depression, severe impairment of hepatic function, severe alcoholic intoxication, delirium tremens [14].

In addition to being a partial agonist of the μ-receptor, buprenorphine is also a potent antagonist of the kappa-type opioid receptors [15]. Moreover, buprenorphine has a strong affinity for delta (δ) opioid receptors (antagonism); however, in light of the recent research, that fact cannot be related to antidepressant effects. It has been found out that the majority of symptoms of opioid withdrawal syndrome are caused by overactivity of kappa receptors. Other opioid drugs have a weak antagonistic effect on kappa receptors. Antagonism towards kappa-type receptors may elicit antidepressant effects by reducing the severity of anhedonia. It has been shown that the increase in kappa receptor activity is associated with depression both in the population addicted to psychoactive substances and the general population as well [16]. Small doses of buprenorphine may have antidepressant effects in patients who have not responded to antidepressant treatment. This action starts soon after the administration of the treatment, the effect of which is similar to that of ketamine [17]. There are hypotheses that buprenorphine may have antidepressant effects by antagonizing kappa receptors or by altering the basic tonus of the endogenous μ receptor. The antagonism of μ receptors alone does not cause antidepressant effect [18]. Depressed patients who do not respond to standard antidepressant treatment may have dysfunctions of the kappa receptor that are similar to opioid addicts. It is still not clear whether buprenorphine affects the concentration of BDNF (brain-derived neurotrophic factor). The potential impact of buprenorphine on the increase in BDNF expression requires further investigation [19].

This paper reviews the results of the latest studies assessing the effect of buprenorphine on the treatment of drug-resistant depression as an add-on therapy o antidepressant treatment. To this end, Medline and PubMed databases were searched using the key words 'buprenorphine' and 'treatment of drug-resistant depression'. The inclusion criteria for the analysis encompassed the years of publication from 1980 to 2017 as well as studies conducted on humans and published in English. The total number of 71 records was found. The results were manually searched by two reviewers. Out of 71 publications, 40 were excluded due to duplications and lack of pertinence. The analysis included 31 studies assessing the efficacy of buprenorphine used as augmentation of depression treatment.

Results

The results of the observational studies show that the treatment with opioids, which are agonists of μ receptors, is associated with a significant and rapid improvement of mental state. It is worth mentioning that the patients with drug-resistant depression also participated in these studies. In 1980, Emrich et al. [20] conducted an observational study in which they demonstrated the antidepressant effect of buprenorphine administered in small doses. The study included 10 patients for whom previous antidepressant medication did not cause an improvement of their mental state.

In the following years, several observational studies confirming the antidepressant effect of various opioid drugs were conducted [21–23]. The anti-depressant effect of

this group of drugs has also been demonstrated in patients with borderline personality disorder [24] and those addicted to opioids and treated with methadone [25]. The attempts to use opioid drugs as antidepressant drugs were, however, rare in the following decades. The antidepressant effect of buprenorphine was the subject of an observational study conducted in 2006 by Gerra et al. [26] and another study conducted in 2008 by Nyhuis et al. [27]. In the study conducted by Nyhuis et al., a low dose of buprenorphine was administered as monotherapy for 7 days in the group of 6 patients hospitalized with the diagnosis of drug-resistant depression. Another observational study was conducted by Karp et al. [28]. Patients with a diagnosis of drug-resistant depression aged 50 years or older were qualified for the study. There were 5 patients who did not respond to treatment with venlafaxine in doses up to 300 mg/d administered for 12 weeks. The lack of response to treatment was defined as ≥ 10 points in the MADRS (*Montgomery-Åsberg Depression Scale*). Additionally, the group of patients who did not respond to two treatments with antidepressants in therapeutic doses was also included in the study (10 patients). Buprenorphine was administered as the augmentation of the standard antidepressant treatment (0.2–1.6 mg/d) for 8 weeks. A significant improvement in the MADRS was observed – baseline mean 27.0 points (*SD* = 7.3) and 9.5 points after 8 weeks of treatment with buprenorphine. The reduction of depressive symptoms was significant already in the first 3 weeks of treatment (mean delta value = – 15.0; *SD* = 7.9). Moreover, treatment with buprenorphine was associated with the improvement in executive functions and learning ability. No significant adverse reactions were observed; the discontinuation of buprenorphine was not associated with the occurrence of withdrawal symptoms.

In 2015, Ehrich et al. [29] published the first randomized placebo-controlled trial assessing the impact of opioid drugs on depression. The researchers administered buprenorphine (a partial μ receptor agonist) together with samidorphan (a μ-type receptor antagonist). The aim of co-administration of buprenorphine and samidorphan was to reduce the risk of addiction without losing the antidepressant effect of buprenorphine. The study included 32 adult people diagnosed with major depression episode according to DSM-IV. The inclusion criteria for the study were as follows: a depressive episode lasting at least 8 weeks and no response to treatment (reduction of symptoms < 50%) after 8 weeks of treatment with an adequate dose of an antidepressant (SSRI or SNRI). Patients with bipolar disorder, psychotic symptoms, personality disorders, and those with an increased risk of suicide were excluded from the study. Patients diagnosed with drug or alcohol addiction within 12 months before being included in the study were also excluded from the study. The patients were randomly assigned to three groups. In the first group, BUP/SAM were administered in the ratio of 8:1 (n = 14), in the second group BUM/SAM 1:1. People included in the third group received placebo (n = 4). All patients were treated simultaneously with antidepressants (SSRI or SNRI). In the population of patients receiving buprenorphine and samidorphan in the ratio of 1:1, higher antidepressant effects were observed. After 7 days of administration of BUP/SAM once a day in the ratio of 1:1, there was a statistically significant reduction in the HAM-D17 (p = 0.032) and an improvement in the MADRS close to statistical significance (p = 0.054) when compared to the placebo group. A combination

therapy with buprenorphine and samidorphan was well-tolerated. The results of this study suggest that the modulation of the endogenous opioid system by administering buprenorphine together with samidorphan may be an alternative in the treatment of patients with an inadequate response to the treatment with antidepressants or with drug-resistant depression.

Another significant study on the use of buprenorphine in the treatment of drug-resistant depression was conducted by Fava et al. [30]. This was a multicenter double-blind placebo-controlled study conducted in the United States. Patients who did not respond to at least one antidepressant treatment were qualified for the study. The inclusion criteria were as follows: age between 18 and 65 years, an episode of depression lasting no more than 24 months; at least 16 points on the HAM-D scale, treatment with a selective serotonin reuptake inhibitor (SSRI) or a serotonin and noradrenaline reuptake inhibitor (SNRI) at appropriate doses for 8 weeks, no response to treatment as a result of one or two antidepressant treatments. The study excluded patients with psychotic symptoms as well as those with a decrease by at least 25% of points or at least 8 points on *the Hamilton Depression Rating Scale* during the initial phase of the study. The study also excluded patients who received psychotherapy within 6 weeks prior to the start of the study or other pharmacological methods of augmentation of treatment, as well as those receiving opioid medicines or naltrexone within 2 months prior to the study. The exclusion criteria also encompassed electroconvulsive therapy during the current episode of depression, suicide attempt in the last 2 years, the history of alcohol or other psychoactive substances dependence in the last 12 months, or the history of opioid addiction. Buprenorphine and samidorphan were administered in the form of a sublingual tablet due to the properties of buprenorphine metabolism (the first-pass effect). The aim of using samidorphan was to reduce a potential addictive effect of buprenorphine associated with agonism to μ-type receptors.

The authors point out that in the studies on depression treatment, there is an excessive reaction to placebo, which may contribute to masking the effects of the drug that shows some antidepressant activity. In the present study, a two-stage comparison model was used to address the problem of over-reaction to placebo. In the first stage, randomization and a double-blind, placebo-controlled trial were used. Patients assigned to the placebo group who did not meet the criteria for the response to treatment were randomly assigned to the active drug or placebo group at the second stage of the study. In the first stage of the study, the participants were allocated to three groups in the ratio of 2:2:9. In the first group, buprenorphine and samidorphan were administered in the ratio of 2:2 (2 mg/2 mg buprenorphine/samidorphan), in the second group the ratio was 8:8 (8 mg/8 mg buprenorphine/samidorphan); in the third group the patients received placebo. In the second stage of the study, the patients who did not respond to placebo were re-assigned to two groups: receiving the active drug or placebo. The subjects who responded to placebo in the first phase of the study were still allocated to the placebo group in the second phase. All patients received a constant dose of antidepressants throughout the treatment period. The antidepressant effect was assessed by the reduction of depression severity on the basis of the 17-point *Hamilton Depression Rating*

Scale (HAM-D), *the Montgomery-Åsberg Depression Rating Scale* (MADRS), and *the Clinical Global Impression Scale* (CGI-S) before and after the 4-week treatment period. When compared to the placebo group, a statistically significant improvement of the mental state in form of the reduction of the scores in three scales (HAM-D: – 2.8; 95% CI: – 5.1 – – 0.6; MADRS: – 4.9; 95% CI: – 8.2 – – 1.6; CGI-S: – 0.5; 95% CI: – 0.9 – – 0.1) was observed in the group which received buprenorphine/samidorphan in the ratio of 2:2. On the other hand, in the group treated with buprenorphine/samidorphan in a ratio of 8: 8, only a statistically insignificant improvement in the mental state was observed. A combined treatment with buprenorphine and samidorphan was well tolerated, no withdrawal symptoms were observed after its discontinuation. The results of this study confirm the hypothesis that the dysfunction of the endogenous opioid system in the CNS would lead to depression. The potentiation of the treatment with buprenorphine co-administered with samidorphan in the population of patients who have not responded to treatment with antidepressant may be an effective treatment method.

The results of the study conducted by Ahmadi and Jahromi [31] also prove antidepressant effect of buprenorphine. The study included opioid-dependent patients with major depressive episode symptoms according to DSM-5. Forty patients were randomized and assigned to three groups: 11 patients (27.5%) received 32 mg, 14 (35%) patients received 64 mg and 15 patients (37.5%) received 96 mg of buprenorphine in a single dose (sublingual route). The severity of depressive symptoms was measured using *the Beck Depression Inventory* before the administration of the drug and on the third day after taking the drug. The results showed a significant reduction in depressive symptoms within each of the three groups ($p = 0.00$). However, there was no significant difference in depressive symptoms reduction across the groups ($p = 0.90$). Therefore, the results show that a single dose of buprenorphine may provide a fast reduction of depressive symptoms in opioid-dependent patients. There were no significant side effects after the administration of the drug.

Recapitulation

The analysis of the conducted studies indicates that dysfunction of the endogenous opioid system in the CNS may be one of the elements of depressive disorders' pathophysiology. Buprenorphine is the drug which affects the opioid system and has a potential antidepressant effect. This drug may have a quite rapid antidepressant effect, thus resembling ketamine. The antidepressant effect of buprenorphine is related to the antagonism to kappa-type opioid receptors and the modulation of μ-type receptors.

In the population of depressed people who have failed to improve in the course of treatment with antidepressants, kappa receptors dysfunctions similar to those observed in opioid-dependent patients may be present.

Buprenorphine added to an antidepressant therapy is usually well-tolerated. The most frequently observed side effects of buprenorphine are excessive sedation and gastrointestinal complaints (nausea and vomiting). Co-administration of buprenorphine and samidorphan may reduce a potential addictive effect of buprenorphine. However,

it should be remembered that except for two randomized placebo-controlled studies conducted in recent years, most of the cited data have limited scientific quality. Future studies on the effectiveness of buprenorphine in the treatment of depression should include larger groups of subjects and should be methodologically correct. Previous studies indicate that buprenorphine has similar efficacy to other methods of treatment augmentation, i.e., administration of lithium, thyroid hormones and atypical antipsychotics.

Many patients with depression do not respond to standard methods of treatment with antidepressants and psychotherapy. The methods of augmentation applied so far do not contribute to the improvement in a large population of patients who suffer from residual depressive symptoms, which result in a significant reduction in the quality of life. The treatment with buprenorphine is relatively well-tolerated. In the light of the conducted studies, buprenorphine administered in small doses and added to antidepressants may have an antidepressant effect in patients who have not responded to treatment with antidepressants as monotherapy.

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