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Review Article
Behavioral Effects of Antibacterial Antibiotics-from Theory to Medical Practice

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Abstract

Antibiotics interact not only with bacteria but also with the human body. The positive and negative effects on the treated human body are particularly complex. These effects occur in both adults and children. There are two major ways in which antibiotics act on behavior: A direct action on the brain and an indirect action by altering the intestinal microbiome and brain-gut axis function. The most important beneficial effects of antibiotics on human behavior and brain activity are reduction of neuronal lesions, improvement of working memory, object recognition and stimulated neurogenesis in ischemic stress and Parkinson's disease (by ceftriaxone), reduction of addiction to cannabinoids and cocaine, but also of alcohol ingestion (by amoxicillin/clavulanate and ceftriaxone). Regarding the negative side effects, the most important are aggravation of depressive states and increased risk of suicide (some quinolones, azithromycin). There are also other effects: Vancomycin can induce cognition disorders, chloramphenicol has a depressant action, gentamicin may exacerbate anxiety, colistin has some neurotoxic effects and isoniazid induces a significant sensitization to seizures. Through enzymatic inhibition, rifampicin accelerates the metabolism of some antipsychotic drugs and reduces their effect, aggravating the condition of some psychiatric patients. When choosing antibiotics for the treatment of various infections, one must take into account first of all the antibiogram but also the behavioral effects of the antibiotics. The purpose of this study was to highlight some of the most important behavioral effects of antibacterial antibiotics and to show their importance for medical practice.

Key words: Antibiotics, behavior, brain-gut axis, microbiota, addiction, depression, quinolones, ceftriaxone

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INTRODUCTION

Antibacterial antibiotics are among the most used drugs in current medical practice. The therapeutic benefit of using antibiotics is very high. Besides the antibacterial action, antibiotics have a significant number of effects on the human and animal body. This group of drugs, in addition to the beneficial antibacterial therapeutic effects, also has an important number of secondary effects. The purpose of this study is to highlight some of the most important behavioral effects of antibacterial antibiotics and to show their importance for medical practice.

The side effects of antibiotics represent between 10-25% of all side effects observed with all drugs used in medical practice. Antibiotics were involved in 19% of all emergency department visits for adverse effects[1]. Some of the under-observed and under-reported side effects of antibiotics are their effects on human behavior. Optimal use of antibiotics is dependent on the identification of primary and secondary focus and also on the identification, reporting and reduction as much as possible of the incident and the severity of side effects. The primary focus is: Destroying or stopping the multiplication of pathogenic microorganisms and the secondary focus is influencing specific infectious syndromes. An only partially known, under-observed and under-reported aspect is the influence of some antibiotics on the patient's behavior. There are two major ways in which antibiotics act on behavior.

A direct action on the brain: Regarding the direct action of some antibiotics on the central nervous system, it occurs through the following mechanisms: Increasing or inhibiting the synthesis of some cerebral neurotransmitters, direct action at the level of some neurotransmitter receptors in the brain, the increase of oxidative stress, influence on some neurotransmitters transporters, inhibition or stimulation on some enzymes, influence cell energy production.

An indirect action by altering the intestinal microbiome: One of the most important adverse effects of an important part of antibacterial antibiotics is the disruption of the intestinal flora. The induction of behavioral changes by some antibiotics by disrupting the normal intestinal flora involves the brain-gut axis and the quantitative and qualitative change of the synaptic neurotransmitters that reach the brain through this axis. The destruction of the normal intestinal flora by some antibacterial antibiotics has multiple consequences (the population of the intestine with pathogenic bacteria, diarrhea, changes in the absorption of some nutrients), but one of the most important effects that are not often given importance is the change in the behavior of the patient who receives antibiotics. There is a possibility that by changing the structure of the intestinal microbiome, the biochemical signals transmitted from the gut to the brain by means of some molecules synthesized by the microbiome may change[2].

There are experimental and clinical studies that show that some antibiotics have an important influence on attention, cognition, depression, reward processes and addiction, anxiety, memory, social behavior, neuroprotection and others. The effects of antibiotics on human behavior can be found in both adults and children. In clinical practice, an important problem is the possibility of confusing some neuropsychiatric symptoms of the disease with the side effects of some antibiotics[3-5].

Negative influence of antibiotics on behavior

Attention deficit: One of the important problems faced by infants and some school children is the lack of attention with serious consequences for school activity. Attention deficit has multiple causes, but there are data that show that antibiotic-exposed infants frequently have problems related to attention deficit. Children have an increased risk of having an attention deficit after perinatal exposure to antibiotics. The use of antibacterial antibiotics is common in the first year of life and occurs in about 70% of children. Attention deficit and hyperactivity disorders are subsequently found significantly more frequently in these children than in those who did not receive antibiotics in the first year of life[6]. In the case of children who received antibiotics in the first six months of life, the tests performed at the age of 11 showed significantly more frequently lower overall cognitive abilities, attention deficit and hyperactivity disorders. Emotional problems were also associated with these[7].

Antibiotics should be used in the first year of life only when necessary and any abuse risks inducing subsequent behavioral changes.

Depression: Major depression is one of the most serious conditions in psychiatric pathology. Its incidence is about 1% of the population (throughout life) and is continuously increasing. The disruption of the intestinal flora is involved in the pathogenesis of depression[8]. The main mechanisms by which the disturbance of the intestinal flora by antibiotics is involved in the pathogenesis of depression (via brain-gut axis) are modification of the cerebral concentration of some neuro mediators, increase in the number of proinflammatory factors

and oxidative stress, both being involved in the mechanism of depression, modification of the synthesis of Brain-Derived Neurotrophic Factors (BDNF).

Another possibility through which some antibiotics can be involved in the mechanism of producing depression is the loss of zinc and magnesium as a result of diarrhea. The deficiency of zinc and magnesium is involved in the pathogenesis of major depression and some of the antidepressant drugs increase the intracellular and plasma concentration of zinc and magnesium[9-11]. Quinolones (new and old)[12] have the most intense effect of inducing or aggravating depressive states. An important problem in connection with the involvement of some antibiotics in the pathogenesis of major depression is the increase in the risk of suicide. This increase in suicide attempts as well as completed suicide was observed especially after the use of some quinolones (ciprofloxacin, moxifloxacin, levofloxacin)[13]. The main supposed mechanisms for suicidal behavior of quinolones are antagonism of GABA brain systems activity, a decrease of brain serotonin level, an increase of NMDA receptor activity, an increase of oxidative stress. Gentamicin (120 mg/kg/day daily) administered for 15 consecutive days in rats produced a depressive-like behavior[14]. After two weeks after stopping the treatment, the depressive-like behavior and anxiety disappeared and the brain concentration values of these neuro mediators normalized[15]. Other antibacterial drugs that induce or worsen pre-existing depression are trimethoprim-sulfamethoxazole, sulfaclozine and azithromycin. Moreover, chloramphenicol has caused depression in some clinical trials[16]. The mechanism of action of chloramphenicol is decreasing the ATP level in the brain. In patients with depression this level is low[17]. Cycloserine, sometimes used in tuberculosis therapy, has a depressant effect. Of course, the results of the experimental studies must be translated with caution in the human clinic, but they cannot be ignored.

Cognitive deficits: The disruption of the normal intestinal flora and the changes that occur at the level of the gut-brain axis influence human behavior and cognition at all ages, but they are of maximum importance in adolescents and in the first years of adult life, when behavioral traits are defined for the rest of life and when the cognitive effort (related to school and university activity) is maximum.

Mice antibiotics treatment from weaning onwards induced disruption of microbiota and cognitive deficits. Depletion of the gut microbial flora from weaning onwards induced various biochemical changes in the brain: Significant reduction of BDNF, significant reduction of oxytocin and vasopressin release and changes in tryptophan metabolism and serotonin activity[18]. The acetate produced by some bacteria is important for synaptophysin synthesis, which is involved in cognition. Synaptophysin is important for the formation of synapses in the hippocampus and possibly in other brain regions[19]. Experimental studies have shown that vancomycin, which is a non-absorbable antibiotic that disrupts the intestinal flora, reduced acetate synthesis but also cognition in rodents[20]. Novel object recognition memory is the most affected in the case of vancomycin administration.

Anxiety: The existing data show that in the case of the use of gentamicin (and possibly also in the case of other aminoglycosides) not only nephrotoxicity and acoustic-vestibular effects but also the degree of anxiety of the patient should be followed. These drugs treatment exacerbates anxiety in highly anxiety-prone male rats[21]. It would be good that in anxious and depressed patients, the administration of gentamicin should be done when it is strictly necessary and the patient should be monitored for at least three days after the treatment.

Other psychiatric and neurological effects: The age of exposure to the antibiotic is important for the adverse behavioral effects of some antibiotics. In experimental studies, the administration of chloramphenicol to adolescent mice showed increased repetitive and compulsive-like behavior. This did not happen in the case of adult mice. The mechanism of action of chloramphenicol (or at least one of the mechanisms) for the production of these effects is that of decreasing brain mitochondrial complex IV activity[22]. The mechanism of action of chloramphenicol (or at least one of the mechanisms) for the production of these effects is that of decreasing brain mitochondrial complex IV activity. Mitochondria are essential for the production of energy at the neuronal level but also in other cells. Neurons are very sensitive to any decrease in energy production. The mechanism of behavioral changes induced by chloramphenicol is based on this decrease in energy production in the brain[17]. In some rare cases, trimethoprim-sulfamethoxazole has induced panic attacks and hallucinations[23]. Rifampicin used in the therapy of the same disease causes faster metabolism of some antipsychotic drugs (through its enzyme induction effect)[24]. Colistin neurotoxic effects were observed in a small number of patients, the most severe of which were epileptic seizures[25]. Some antituberculous drugs induce dizziness. Isoniazid induces a significant sensitization to seizures by decreasing the concentration of GABA in the brain.

In addition to the direct action of some antibiotics on the brain, these substances can also influence the functioning of the brain and human behavior indirectly, by changing the permeability of the blood-brain barrier[26]. The gut microbiome has also been suggested to regulate reward processes in the brain[27].

The administration of antibiotics to women who breastfeed the child changes the taste of the milk and thus the eating behavior of the child changes, often refusing breast milk[28].

Experimental studies showed the influence of some antibiotics on social behavior. Perinatal exposure to azithromycin of zebra finches (*Taeniopygia guttata*) reduced affiliative behavior[29].

Psychotic episodes have been reported following the clinical use of metronidazole[30]. Clarithromycin caused hallucinations in some patients[31,32]. The mechanism of these psychotic episodes is not known, but it is possible that they are induced by disturbances in the activity of the cerebral aminergic systems after the disruption of the normal intestinal flora. It was found that *Lactobacillus* synthesizes dopamine that reaches the brain via the brain-gut axis. Disruption of the normal intestinal flora by some antibiotics can change the concentrations of some cerebral synaptic neurotransmitters[33,34].

Positive effects of antibiotics on behavior

Neuroprotection: The most important positive effect is the neuroprotective effect of some beta-lactam antibiotics[35]. Animal neuronal mortality in experimental models of brain deprivation of oxygen and glucose was reduced by ceftriaxone. There are three mechanisms by which ceftriaxone has neuroprotective effects in conditions of cerebral hypoxia: Reduction of pro-inflammatory cytokine production (interleukin-1 beta and TNF-alpha), decrease of oxidative stress[36] increasing the expression of the transporter for glutamate at the glial and neuronal level. An increased level of this transporter decreases the exotoxicity of glutamate[37]. Excess of glutamate by NMDA receptors stimulation is involved in the disruption of neuronal activity. Ceftriaxone does not have a favorable effect only in conditions of cerebral hypoxia. In rats with an experimental model of Parkinson's disease (relatively close to human Parkinson's disease in terms of the pathogenic mechanism), ceftriaxone administered for 14 days determined the reduction of neuronal lesions in the hippocampus and dentate gyrus, improved working memory and object recognition and stimulated neurogenesis[38]. Ceftriaxone by protecting dopaminergic neurons against the toxic action of 6-hydroxydopamine determines the improvement of the symptoms of experimental Parkinson's disease in rats[39]. The mechanism of the protective action of ceftriaxone in ischemic stress and in Parkinson's disease was shown in Fig.1.

Minocycline prevented the degeneration of dopaminergic neurons in nigro-striatal structures in experimental models of Parkinson's disease[40].

In experimental models of Huntington's disease and amyotrophic lateral sclerosis, minocycline had neuroprotective effects and its clinical use was recommended[41]. The mechanism by which minocycline can improve symptoms in Huntington's disease (in experimental but also in clinical trials) is the inhibition of caspase and nitric oxide synthesis in the brain[42,43].

Reward system and addiction: The action of some antibiotics at the level of the reward system is also important. The reward system is involved in many normal human activities (food intake, sexual activities, games and others). The normal functioning of the reward system is essential for normal human behavior. Some beta-lactam antibiotics have actions at the level of the reward system and influence human and animal behavior through this mechanism. Malfunction of the reward system is essential in all addictions. Amphetamine is one of the most addictive substances used by a large number of people. The increased activity of the cerebral glutamatergic system is involved in the seeking behavior of several addictive drugs (heroin, amfetamine cocaine and others). In experimental studies, ceftriaxone reduces amphetamine-induced drug seeking[44]. Amphetamine, methamphetamine and other addictive psychostimulant substances disrupt glutamate homeostasis in some regions of the brain (nucleus accumbens, substantia nigra). In essence, the level of extrasynaptic glutamate increases as a result of the decrease in GLT1 activity, which is the glutamate transporter that removes extrasynaptic glutamate. Amfetamine, methamphetamine and other psychostimulant drugs reduce GLT1 transporter expression. Administration of ceftriaxone blocked amphetamine-induced reinstatement and restores the normal expression level of GLT1 in the rat's brain This antibiotic reduces the intensity of ethanol withdrawal through up-regulation of glutamate transporter EAAT2[45]. Ceftriaxone also alleviated in studies on mice the hyperlocomotion caused by cocaine and reduced the behavioral sensitization determined by this highly used addictive substance. The use of this beta-lactam antibiotic has been suggested in the treatment of cocaine abuse[46]. Minocycline reduces the rewarding effects of dextroamphetamine in human clinical practice. The

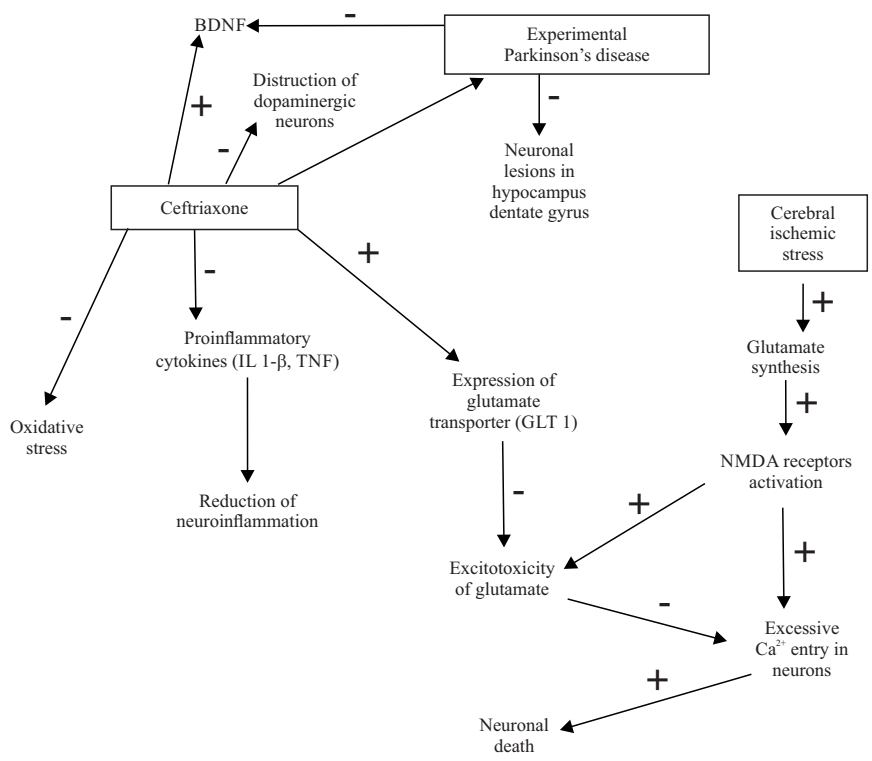

Fig. 1: Mechanism of the protective action of ceftriaxone in ischemic stress and in Parkinson's disease

mechanism of action is largely different from the action of beta-lactams at the level of the reward system. This drug reduces the synthesis and release of dopamine in the reward system.

Ampicillin/sulbactam upregulate GLT-1, cystine/glutamate transporter (xCT) and glutamate aspartate transporter (GLAST) in the nucleus accumbens and amigdala. In this way, ampicillin/sulbactam administered during the extinction phase of the conditioned place preference method (CPP) attenuated induced reinstatement. As a result of these actions, the dependence on cannabinoids is also reduced[47]. Amoxicilline/clavulanate reduced ethanol intake in alcohol-preferring rats also by increasing GLT-1 expression[48]. The biochemical mechanisms of some antibiotic's action on the reward system and addiction to some substances were presented in Fig. 2.

Pain: Unlike other antibiotics, minocycline also reduces the intensity of pain[20].

Attention deficit and hyperactivity disorder: The infection produced by Group A *Streptococcus* is associated in some cases with psychiatric disorders such as attention-deficit/hyperactivity disorder or obsessive-compulsive disorder. Exposure of rats to ampicillin causes a reduction of these pathological behavioral changes simultaneously with a reduction in IL-6 and IL-17 levels[49].

Depression: Linezolid (an oxazolidinedione antibiotic) administered at a dose of 5-40 mg kg^{-1} in mice has a significant dose-dependent antidepressant effect. The mechanism by which this effect is produced is related to the fact that this antibiotic increases the level of cerebral norepinephrine. Linezolid inhibits MAO-A (Monoamine Oxidase-A), a key enzyme in norepinephrine and serotonin metabolism and in this way causes an increase in the amount of norepinephrine and brain serotonin. In addition to the antidepressant effect, linezolid also has an anxiolytic effect[50]. Also, minocycline has an antidepressant effect, the mechanism of which is not clear, but it is considered to be produced at the level of cerebral microglia[20].

Memory and Alzheimer's disease: Regarding memory in patients with various diseases but who do not suffer from post-traumatic stress, clinical studies done, for example, in patients with Lyme disease showed that the administration of ceftriaxone for 2 weeks or doxycycline and clarithromycin for 12 weeks did not significantly change cognitive performance[51]. The D-cycloserine improved long-term memory in rodents[52].

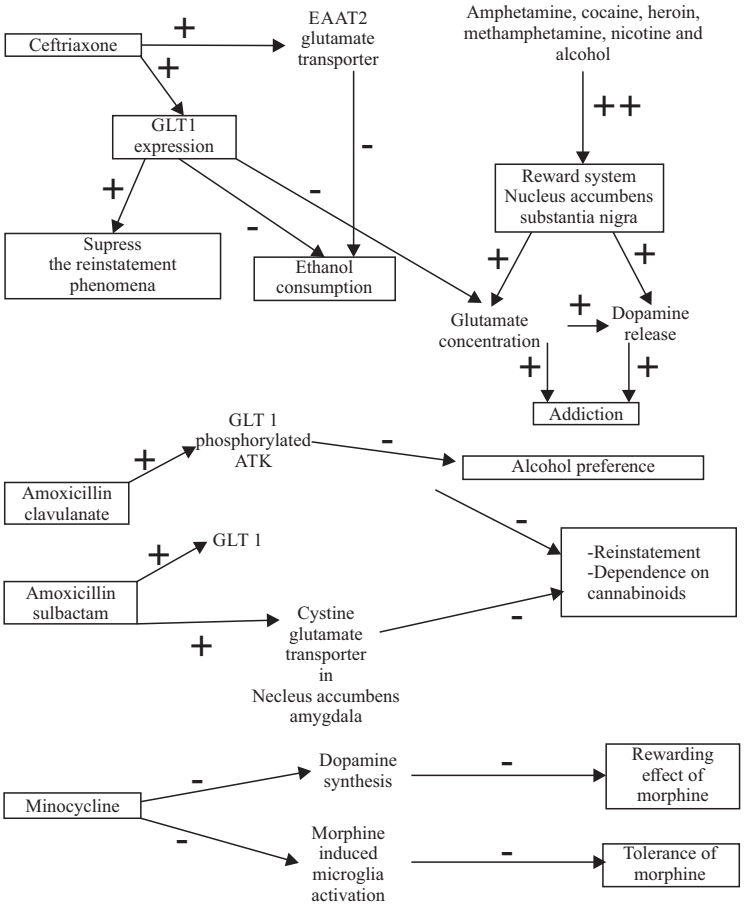

Fig. 2: Some antibiotics action on the reward system and addiction

Dementia is one of the most serious diseases in the human clinic. The most severe and at the same time frequent among them is Alzheimer's disease. The essential pathogenic mechanism of Alzheimer's disease is the accumulation of neuronal and synaptic amyloid-β oligomers. Rifampicin reduces the synthesis and neuronal and synaptic accumulation of these oligomers (Aβ, tau and α-synuclein). There is also a dose-dependent effect of rifampicin inhibiting microglial activation, inhibiting cytochrome c release from the mitochondria and reducing caspase 3 activation in the hippocampus[53].

Although, Alzheimer's disease cannot be accurately reproduced in animals by the existing experimental models, it is important to note that minocycline, in the experimental model of Alzheimer's disease produced by the administration of Aβ1-42 in rats, reduced depression and decreased the level of the second proinflammatory cytokines (TNF-alpha and IL-1beta) in the hippocampus. The concentration of these cytokines is significantly increased in this experimental model of Alzheimer's disease, but also in the human clinical disease[54]. In the experimental model of Alzheimer's disease (produced with scopolamine), minocycline reduced neuroinflammation, cholinergic dysfunction and improved cognition[55].

These effects have a beneficial influence on human behavior and the clinical use of minocycline has been suggested for this purpose. There are no known data on the action of other tetracyclines at the level of behavior, nor the reason why, from this group of drugs, only minocycline has these effects that do not seem to be related to its antibacterial action.

Due to the increase in the incidence of diseases that influences memory the investigation of the causes of memory changes and the influence that various drugs with different chemical structures and with various therapeutic uses have on memory has intensified.

Fear: The increased level of these cytokines in the hippocampus is involved in the mechanism of producing fear. These cytokines are synthesized by cerebral microglia and their synthesis is stimulated by IFN-alpha[56]. Minocycline

administered together with IFN-alpha prevents the effect of interferon on fear while reducing the synthesis of proinflammatory cytokines.

Cycloserine has an important effect of reducing fear induced by external conditioning in mice or rats. This effect is only obtained by intracranial administration at the level of the hypothalamus and it is not clear whether this effect could be translated into the human clinic. This antibiotic is a partial agonist of the N-methyl-D-aspartate glutamate receptor and it is considered that this is the mechanism of fear reduction, but it is not clear why only intra-hippocampal treatment inhibits fear and not the administration in other regions of the brain such as the amygdala. A special situation is the fear of memory retention. One of the important factors necessary to reduce fear is to diminish it. In clinical studies, a reduction of fear memory retention in those participants who were trained under doxycycline. The mechanism of action of doxycycline, in this case, is the inhibition by this antibiotic of the extracellular enzyme Matrix Metalloproteinase-9 (MMP-9)[57]. This enzyme has an important role in memory, being necessary for synaptic reconfiguration. Doxycycline inhibits this enzyme and thus reduces fear in post-traumatic stress.

Schizophrenia: In clinical studies, d-cycloserine improved cognitive deficits and reduced some of the negative symptoms in patients with schizophrenia[58]. However, these results are controversial as there are studies that did not show an improvement in negative symptoms in schizophrenic patients.

CONCLUSION

The use of antibacterial antibiotics must be done correctly and limited to what is strictly necessary. Behavioral changes in patients receiving antibiotic treatment must be followed and reported. The abuse of antibiotics administered to pregnant women, breastfeeding women and children in the first years of life can have important long-term behavioral effects. In the future, more clinical and experimental studies are needed to highlight the behavioral effects of all groups of antibiotics used in practice, as well as for the detailed identification of their production mechanisms. The action of antibacterial antibiotics on the human body and human behavior must be given more importance in clinical practice. Knowledge of these actions helps a more correct use of antibiotics.

SIGNIFICANCE STATEMENT

This study shows the existence of numerous behavioral effects of antibacterial antibiotics whose frequency and importance are often underestimated in medical practice. A better knowledge of these effects will have the immediate effect of an increase in their diagnosis. The study shows the need for increased attention to the side effects of antibacterial antibiotics, effects different from the antibacterial action of these substances. The paper also shows the importance of knowing the associated pathology that the patient with bacterial infection has and the need to use antibiotic therapy not only in relation to the bacterial sensitivity to antibiotics but also taking into account the behavioral effects of antibiotics. The work will contribute towards the better use of antibacterial antibiotics.

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