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Retrospective analysis of the use of benzodiazepines in anxiety disorders

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Abstract: *in times of great social shocks, economic crises, epidemics and pandemics, military conflicts, usually can be observed the spread of such a group of psychological diseases as anxiety disorders (ADs). ADs are a widespread group of human behavior disorders characterized by a wide range of symptoms that cause significant changes in behavior and reduce the patient's quality of life and may lead to deterioration of his social activity. This group of diseases includes a number of behavioral disorders, the characteristic feature of which is the patient's feeling of fear and/or anxiety, which is usually an excessive and unmotivated reaction to a stimulus or an event that caused them. As a result of the analysis of available data, it was revealed that benzodiazepines are actively used as second-line drugs in ADs pharmacotherapy. The pharmacological effect of this group of medications is associated with an agonistic interaction with $GABA_A$ receptors of the central nervous system. It has also been established that this group of drugs is an effective element of complex therapy together with antidepressants or as monotherapy of such ADs as generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), selective mutism (SM) etc. During ADs therapy with benzodiazepines, a number of side effects, such as excessive sedation, cognitive impairment, and psychomotor disorder of coordination of movements, have been identified. This group of drugs requires special caution when used in elderly patients due to possible excessive sedation and impaired cognitive function. But if the recommended course of treatment is followed, benzodiazepines are a safe to use group of drugs that have a wide spectrum of pharmacological action. The purpose of this work was to study the available data on the pharmacological properties of benzodiazepine anxiolytics for the purpose of their use in the pharmacotherapy of diseases belonging to the ADs group. To achieve this goal, publications and articles devoted to ADs pharmacotherapy methods were reviewed and analyzed. Materials were searched using the databases Pud Med and Google Scholar.*

Keywords: antidepressive agents, anxiolytics, anxiety disorders, benzodiazepines, pharmacotherapy.

Introduction

In the modern world, the problem of the therapy of psychological disorders is attracting more and more attention from health care professionals due to the steady trend of their spread among the population of most countries of the world. In times of great social shocks, economic crises, epidemics and pandemics, military conflicts, usually can be observed the spread of such a group of psychological diseases as anxiety disorders (ADs).

According to the modern classification of ICD-11, this group of disorders represents a wide range of diseases, such as generalized anx-

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iety disorder (GAD, 6B00), panic disorder (PD, 6B01), agoraphobia (6B02), social phobia (SP, 6B04), separation anxiety disorder (SAD, 6B05), selective mutism (SM, 6B06), hypochondriasis (6B23.0-6B23.Z), substance-induced anxiety disorders (6C40.71- 6C4G.71), Secondary anxiety syndrome (SAS, 6E63) (WHO, 2022).

A key feature of ADs is the presence of the patient's feelings of fear and/or anxiety, which are usually an excessive and unmotivated response to the stimulus or event that caused them. The anxious state of the patient can last for several weeks, months and years after the end of the stimulus that caused such a state. At that time, anxiety in a healthy person passes much faster. In addition, most ADs have their own characteristics of the course and stimuli that cause them. For example, PD is characterized by the development of short-term panic attacks in the patient, accompanied by an accelerated heartbeat, lack of sensitivity in the limbs, nausea or vomiting and fear of death (WHO, 2022, Copchak O. O. 2018, Oros & M. M., Sabovchyk A. Ya., 2019). In turn, GAD manifestations are more chronic: sleep disturbances, irritability, nausea, stomach disorders, subjective feeling of anxiety, dry mouth (WHO, 2022, Copchak, O. O. 2018). Other ADs, such as social anxiety disorder (CTP, 6B04) and selective mutism (CM, 6B06) lead to deterioration of the patient's social life and his communication skills (WHO,2022, Avramchuk O. 2018, Schiele M. A. & Domschke K., 2021).

Another feature of ADs is the high degree of comorbidity with other psychological disorders of other classification groups (depression, obsessive-compulsive disorder, schizophrenia, etc.), which complicates the diagnosis of the disease in an individual patient (WHO, 2022).

Some ADs are common among patients of specific age groups. As an example, SM (6B06) and separation anxiety disorder (SAD, 6B05) are common among children and adolescents (up to 18 years) (Schiele M. A. & Domschke K., 2021).

Thus, ADs is a widespread group of human behavior disorders, which is characterized by a wide range of symptoms that reduce the patient's standard of living and can lead to deterioration of his social activity. Therefore, the question of ADs therapy is becoming an increasingly relevant problem in the field of health care.

Aim

The task of this work was to study the available data on the pharmacological properties of benzodiazepine tranquilizers with the aim of using them in the pharmacotherapy of diseases belonging to the AD group.

Materials and methods

Publications and articles devoted to ADs pharmacotherapy methods were reviewed and analyzed in order to determine the role of benzodiazepines in the treatment scheme of this group of diseases. Materials were searched using the databases Pud Med and Google Scholar.

Review and discussion

Pharmacotherapy is an integral part of ADs treatment along with psychological therapy. Medicines began to be actively used in ADs therapy almost immediately after the discovery of this group of disorders.

Antidepressants belonging to the groups of selective serotonin reuptake inhibitors (SSRIs) and Serotonin–norepinephrine reuptake inhibitors (SNRIs) are used as first-line agents in the pharmacotherapy of ADs (Copchak O. O., 2018, Garakani et al., 2020, Karvatska N. S., Burla Sh. S. & Tkach S. D., 2020). However, therapy with the mentioned pharmacological means is characterized by the use of medications for a long time, the slow development of the therapeutic effect, the presence of side effects (gastrointestinal disorders, sedation, insomnia, sexual dysfunction, dry mouth, diarrhea or constipation) (Strawn J.R., Mills J. A., Sauley B. A. & Welge J. A., 2018).

Therefore, benzodiazepines are actively used as second-line drugs in ADs pharmacotherapy. This group of medicines has been actively used in medical practice since the middle of the 20th century. On the pharmaceutical market of Ukraine, this group of medications is represented by medications, which are shown in the Table 1.

During more than half a century of use, a large volume of data on the effectiveness of pharmacotherapy, side effects, and metabolism of this group of drugs has been accumulated. The pharmacological effect of this group of agents is associated with an agonistic interaction with $GABA_A$ receptors of the central nervous system (Gomez A. F., Barthel A. L. & Hofmann S. G., 2018).

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Table 1

Trade name	Active substance	Manufacturer
Diazepam-3H	Diazepam	"People's Health" LLP, Kharkiv
Lorazepam-3H	Lorazepam	
Alprazolam-3H	Alprazolam	
Sibazon IC	Diazepam	SLC "InterChem", Odesa
Gidazepam IC	Gidazepam	
Levana IC	Levana	
Phenazepam IC	Phenazepam	
Clonazepam IC	Clonazepam	
Diazepex	Diazepam	AS "Kalceks", Latvia

Unlike most antidepressants, the therapeutic effect of benzodiazepines begins much faster, although it lasts for a shorter time (Garakani, A. et al. 2020). The pharmacological effect is observed within 1-2 days after the start of administration (Burchinskii, S. G., 2018).

A number of long-acting benzodiazepines (diazepam, clonazepam, and lorazepam) are actively used in the pharmacotherapy of GAD (Strawn, J. R., Geracioti, L., Rajdev, N., Clemenza, K. & Levine, A. 2018). Due to a long half-life, these drugs are able to maintain a high concentration in the blood plasma for a longer time, which is an important measure for the effectiveness of drugs during the treatment of GAD.

However, there is conflicting data regarding long-term (more than 4 weeks) benzodiazepine therapy. Some researchers believe that due to the risk of developing addiction and side effects, the use of this group of drugs in the treatment of GAD and other ADs with a chronic course is appropriate only in the absence of the effect of SSRIs and SNRIs (Karvatska N. S. et al., 2020). At the same time, there is a point of view according to which the long-term use of benzodiazepines is justified if there is a pronounced therapeutic effect during the first 4 weeks of treatment (Rickels K. & Moeller H. J., 2019). Therefore, drugs of this group are used for short-term therapy of AD.

Benzodiazepines with a pronounced anticonvulsant and muscle relaxant effect, such as clonazepam and midazolam can be used to reduce the somatic manifestations of AD, such as tremors or muscle spasms, which are very common symptoms in patients with PD (Fogari R. et al., 2019).

Benzodiazepines can be used together with antidepressants in the ADs pharmacotherapy scheme. Thus, it was established that the simultaneous appointment of sertraline (SSRI) and clonazepam leads to a decrease in the side effects of the antidepressant and an increase in the pharmacological effect of both drugs (Hovenkamp-Hermelink J. H. et al., 2021).

However, this class of drugs also has a number of disadvantages. A number of side effects, such as excessive sedation, cognitive impairment, and psychomotor disorder of coordination of movements, have been identified during ADs therapy with benzodiazepines. This group of drugs requires special caution when used in elderly patients due to possible excessive sedation and impaired cognitive functions (Gomez A. F., Barthel A. L. & Hofmann S. G., 2018). In addition, the long-term use of benzodiazepines by patients of this age group is associated with a high probability of developing dementia, tolerance to the drug, or even addiction (Garakani A. et al., 2020).

Also, the ability of diazepam to affect blood pressure and heart rate, which can be observed at night, has been revealed. At the same time, no changes in blood pressure were observed during

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the day. A similar phenomenon is usually observed in elderly patients (Fogari R. et al., 2019). There is a point of view that a similar phenomenon is explained by the increased volume of distribution of diazepam in the body of elderly patients, although a similar effect of the drug is observed in patients of other age groups (Fogari R. et al., 2019, Costa A. et al., 2018).

Another significant disadvantage of benzodiazepines is their ability to affect the ability to drive and cause cognitive impairment (Jongen S., Vuurman E. F. P. M., Ramaekers J. G. & Vermeeren A., 2018).

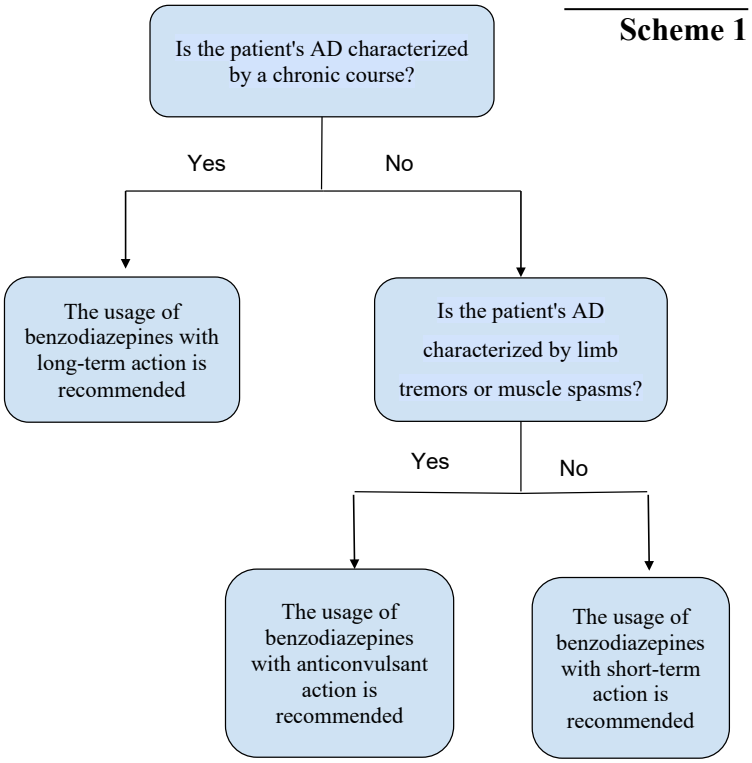
This pharmacological group of drugs has a number of contraindications for use, which must be taken into account when prescribing the drug. Most benzodiazepines are characterized by the following number of contraindications:

1. *History of abuse of psychoactive substances or drugs by the patient*. Patients with a history of addiction to opioids and other psychoactive substances or medications have been found to be more likely to develop tolerance to benzodiazepine anxiolytics (Gomez A. F., Barthel A. L. & Hofmann S. G., 2018). Therefore, the appointment of the future remedy requires a preliminary analysis of the patient's history of addiction to psychoactive substances.
2. *Liver and/or kidney function disorders*. In the case of liver/kidney failure, the use of agents whose active substance has a long half-life (diazepam, midazolam, clonazepam, etc.) requires special caution (Mathé A. A., Michaneck M., Berg E., Charney D. S., & Murrough J. W., 2020). In the case of drugs that have a pharmacologically active metabolite (midazolam, diazepam, etc.), it can lead to an increase and prolongation of the therapeutic effect (Marçon F. et al., 2018).
3. *Sensitivity to the active substance or components of the medication.*

Conclusions

Thus, benzodiazepines may become a possible alternative to antidepressants in the pharmacotherapy of ADs. However, this group of drugs has a number of disadvantages, including the presence of side effects and a limited recommended course of treatment due to the probable development of tolerance and/or addiction to the drug. But if the recommended course of treatment is followed, benzodiazepines are a safe to use group of drugs that have a wide spectrum of pharmacological action. A general tactic for the use of benzodiazepines during AD has been proposed in Scheme 1. Thanks to this, it becomes possible to prescribe a drug capable of eliminating the individual manifestations of ADs of an individual patient. Agents with anxiolytic and anticonvulsant effects (midazolam, clonazepam) may be the drug of choice for PD to eliminate limb tremors, muscle spasms, and other manifestations of panic attacks.

Scheme 1



Benzodiazepines with a long half-life are able to provide a pharmacological effect that will persist for a long time, which in turn can be useful in the treatment of GAD and other ADs with chronic symptoms.

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Consent to publish

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

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Ретроспективний аналіз застосування бензодіазепінів при тривожних розладах

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Анотація*:* у період великих соціальних потрясінь, економічних криз, епідемій і пандемій, військових конфліктів зазвичай спостерігається поширення такої групи психологічних захворювань, як тривожні розлади (ТР). ТР — широко поширена група розладів поведінки людини, що характеризується широким спектром симптомів, які викликають суттєві зміни в поведінці та знижують якість життя пацієнта, можуть призвести до погіршення його соціальної активності. До цієї групи захворювань входить низка поведінкових розладів, характерною рисою яких є відчуття страху та/або тривоги у пацієнта, яке зазвичай є надмірною та невмотивованою реакцією на подразник або подію, що їх викликала. У результаті аналізу наявних даних виявлено, що бензодіазепіни активно використовуються як препарати другого ряду у фармакотерапії ТР. Фармакологічний ефект цієї групи препаратів пов'язаний з агоністичною взаємодією з $ГАМК_А$-рецепторами центральної нервової системи. Також встановлено, що дана група препаратів є ефективним елементом комплексної терапії разом з антидепресантами або як монотерапія таких ТР, як генералізований тривожний розлад (ГТР), панічний розлад (ПР), соціальний тривожний розлад (СТР), селективний мутизм (СМ) тощо. Під час терапії ТР бензодіазепінами може виникнути ряд побічних ефектів, таких як надмірна седація, когнітивні порушення та психомоторні розлади. виявлено координацію рухів. Ця група препаратів потребує особливої обережності при застосуванні пацієнтам літнього віку через можливу надмірну седативну дію та порушення когнітивних функцій. Але при дотриманні рекомендованого курсу лікування бензодіазепіни є безпечною для застосування групою препаратів, які мають широкий спектр фармакологічної дії. Метою даної роботи було вивчення наявних даних про фармакологічні властивості бензодіазепінових анксіолітиків з метою їх використання у фармакотерапії захворювань групи ТР. Для досягнення поставленої мети було розглянуто та проаналізовано публікації та статті, присвячені методам фармакотерапії ТР. Пошук матеріалів здійснювався за допомогою наукометричних баз даних Pud Med та Google Scholar.

Ключові слова*:* антидепресивні засоби, анксіолітики, тривожні розлади, бензодіазепіни, фармакотерапія.