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Research Article

# Off-label short-term use of thiocolchicoside (Tiyozid®) in the clinical therapy of fibromyalgia

Valentina Reshkova[1], Simeon Monov[2], Alexander Mandadjiev[3]

1 *"St. Ivan Rilski" University Hospital, Sofia, Bulgaria*
2 *"St. Anna" University Hospital, Sofia, Bulgaria*
3 *Nobel Pharma Bulgaria, Sofia, Bulgaria*

Corresponding authors: Valentina Reshkova (v_reshkova@abv.bg); Alexander Mandadjiev (alexander.mandadjiev@gmail.com)

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## Abstract

**Summary:** Fibromyalgia (FM) is a complex, chronic, nondegenerative musculoskeletal disorder of unknown etiology, and it requires a different clinical approach for every patient.

**Objectives:** The present clinical follow-up observes the effect of the central-acting myorelaxant thiocolchicoside (Tiyozid®) on clinical manifestations in patients with primary fibromyalgia.

**Methods:** The following article presents a prospective clinical follow-up in eighteen ambulatory women with primary fibromyalgia observed in 41 days.

**Results:** A significant difference between the 1st and 41st day of treatment with thiocolchicoside (Tiyozid®) 4 mg tablets in the mean number of pain points (15.4 ± 1.9 vs. 13.17 ± 1.5, $p < 0.05$), an increase in pain threshold (2.37 ± 0.4 to 2.58 ± 0.3, $p > 0.05$), and a decrease in the degree of chronic fatigue (7.1 ± 0.8 vs. 3.5 ± 1.3, $p < 0.05$). On the 41st day, the overall impact of treatment with thiocolchicoside on quality of life showed a significant improvement (37.5 ± 11 vs. 28 ± 8, $p < 0.05$).

**Conclusion:** As a short-term therapy, thiocolchicoside (Tiyozid®) has a positive effect on clinical manifestations in patients with primary fibromyalgia, which affects everyday activities and improves their quality of life.

## Keywords

fibromyalgia, pain, hypertonicity, myorelaxants, thiocolchicoside

## Introduction

Chronic pain of moderate to severe intensity occurs in 19% of adult Europeans, seriously affecting the quality of their social and working lives (Breivik et al. 2006). About half of all patients with musculoskeletal pain have fibromyalgia (FM). Fibromyalgia is a complex, chronic, nondegenerative musculoskeletal disorder of unknown etiology. It is widespread and covers different age groups, primarily between 20 and 50 years. The global prevalence of the disease is estimated to be between 2 and 4% (Berwick et al. 2022). The total prevalence of fibromyalgia in the Eurozone was calculated as 2.64% (Kocyigit and Akyol 2022). Women are affected more than men, in a ratio of 9:1 to 20:1, and there is no defined ethnic predisposition.

There are no epidemiological data on the prevalence of FM in Bulgaria (Reshkova 2013).

Fibromyalgia is characterized by diffuse pain lasting longer than three months and with multiple painful regions, particularly in the axial skeleton. Although the pathogenesis of FM is not completely understood, alterations of the central nervous system (CNS) may contribute to the chronic pain of FM (Di Franco et al. 2010; Siracusa et al. 2021). In addition, fibromyalgia is associated with numerous other symptoms, including fatigue, cognitive dysfunction, nonrestorative sleep, depression, anxiety, and muscle stiffness. Each of these central symptoms—sleep disturbances, fatigue, and stiffness—is present in more than 75% of fibromyalgia patients (Wolfe et al. 1990).

Despite the clear diagnostic criteria for fibromyalgia, this disorder is not properly identified by primary care providers (PCPs). 63% of them manage patients with fibromyalgia after diagnosis, and 37% of PCPs refer patients with fibromyalgia to a specialist, typically a rheumatologist, for diagnosis. (Pang et al. 2021).

In the clinical approach of FM, rheumatologists aim to treat chronic pain and increased muscle tone (hypertonicity) by following several steps: assessing the cause of these symptoms related to the intensity of nerve hyperexcitability and ischemia; assessing the pathophysiological mechanisms; assessing the clinical aspect of pain and hypertonicity; and treating the pain and increased muscle tone.

A lowered pain threshold at tender (painful, myofascial, trigger) points remains the main clinical feature of fibromyalgia. To be diagnosed, the patients need to be evaluated according to the 2016 ACR criteria based on the presence of chronic widespread pain in more than 7 out of 19 body areas over the past 3 months and accompanying clinical symptoms (fatigue, sleep without invigoration, cognitive symptoms) or 7 higher scores from the combined scale (Severity Scale, SS) (Wolfe et al. 2016; Berwick 2022). The second criterion (revised in 2016) is that the pain must be measured with a dolorimeter in at least 11 of 18 painful points (Reshkova 2013; Wolfe et al. 2016).

In addition, the trigger points in muscles are recognized as powerful sources of peripheral nociceptive impulses that can profoundly influence the sensory processing of painful messages at the central level (Xu et al. 2010). The activation of myofascial (trigger) points in FM causes painful muscle solidifications called "myogelosis" to appear in their place and can be palpated. They result from the vicious cycle of spasm-ischemia-pain-spasm. (Windisch et al. 1999; Reshkova 2013; Koleva et al. 2015). Muscle spasms and muscle shortening due to trigger points impair joint function and mobility. Stiffness of muscles and joints is problematic for most FM patients (Wolfe et al. 1990).

The conventional medical therapies that target the pathology of FM produce limited benefits. They remain mainly pharmacological and tend to treat the symptomatic aspects of various disorders reported by the patient. The statistics showed the fact that 90% of people with fibromyalgia also turn to unconventional medicine to manage their symptoms (Siracusa et al. 2021).

Reduction in pain and hyperalgesia was observed following treatment with antidepressants, opioids, and glutamate receptor antagonists, while no effect was observed with nonsteroidal anti-inflammatory drugs (NSAIDs) (Siracusa et al. 2021).

As an additional therapy or alternative approach, the attending physician should look for the inactivation of active trigger points in the muscles, which may serve as peripheral generators of fibromyalgia pain, as Giamberardino et al. (2011) suggest. In that aspect, one common concomitant therapy is the administration of muscle relaxants, even though their efficacy as an adjuvant therapy in FM is controversial.

Myorelaxants are used to treat nociceptive and mixed pain caused by muscle spasms (hypertonicity) and can be administered as an effective adjunct in treating patients with significant stiffness.

Central-acting myorelaxants do not directly affect the muscle, neuromuscular synapse, or motor nerves. Their mechanism of action varies from the interaction of GABA receptors (baclofen, thiocolchicoside, diazepam), 5-HT2 receptor antagonists (cyclobenzaprine), NMDA and acetylcholine receptor antagonists (orphenadrine), α2 (presynaptic) adrenergic receptor agonists (tizanidine), to blocking voltage-gated sodium and calcium channels (tolperisone).

Myorelaxants are used off-label in rheumatology practice to treat tension-type headaches, myofascial pain syndrome, fibromyalgia, relaxing the contraction of pericranial muscles, reducing the formation of myogelosis because of spasms at trigger points, back and low back pain resulting from contraction of the paravertebral muscles, traumas, and contraction of sore muscles. Thus, they reduce muscle hypoxia and spasm, breaking the vicious cycle of spasm-pain-spasm.

In the Bulgarian Pharmacotherapeutic Guidelines for the Treatment of Neurological Diseases 2023, the central-acting myorelaxant tizanidine (12–24 mg daily) is the medication of second choice for patients with fibromyalgia and back pain. It suppresses polysynaptic spinal mechanisms associated with increased muscle tone by affecting the release of excitatory amino acids from interneurons.

According to Boomershine (2010), benzodiazepines should be avoided in FM patients due to significant addiction potential and worsening of sleep architecture. There is no evidence to support the usage of antispasmodics (such as baclofen or dantrolene) in FM, but patients with spasticity may benefit from these agents.

Regarding the safety profile of the central-acting myorelaxants, the incidence of drowsiness, dizziness, and other side effects is high, which disturbs the patients and compromises the treatment.

Thiocolchicoside (presented in Bulgaria by the trade name Tiyozid® of Nobel Pharma Bulgaria), a semi-synthetic derivative of naturally occurring colchicoside, has long been used as a myorelaxant in humans. It is a central-acting muscle relaxant with additional anti-inflammatory and analgesic properties. It has been shown to interact as an antagonist with gamma-aminobutyric acid (GABA) type A receptors ($GABA_A Rs$) and acts as an agonist of strychnine-sensitive glycine receptors in the central nervous system (Carta et al. 2006). The interaction with the glycine receptors in the

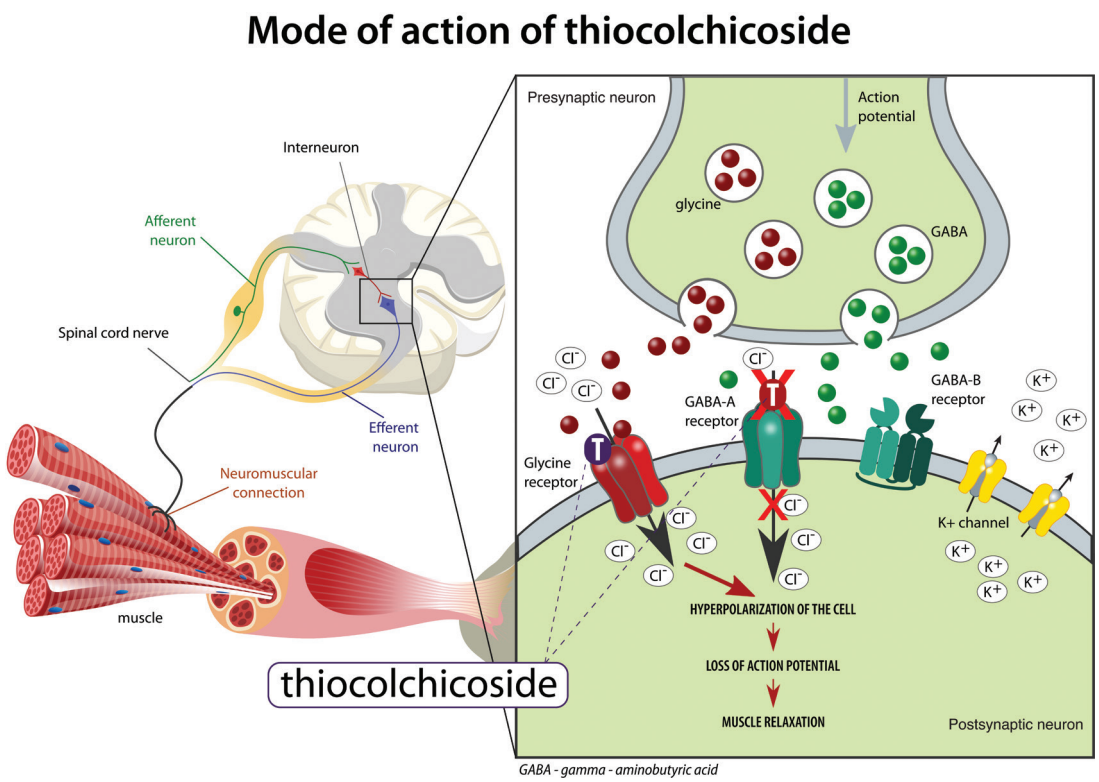


**Figure 1.** Mechanism of action of thiocolchicoside.

spinal cord and brainstem may provide a possible mechanism for myorelaxant activity (Fig. 1). Concerning its safety profile, there is no observed significant sedative effect with thiocolchicoside treatment in the studies that led to discontinuation of therapy (Cimino et al. 1996; Aksoy et al. 2002; Carta et al. 2006; Umarkar 2011; SmPC Tiyozid).

In the literature, thiocolchicoside has been considered in some myorelaxant reviews for adjuvant treatment of low back pain or myofascial pain syndrome (Desai et al. 2013). Still, there has been no study of its use in fibromyalgia. The closest condition in which it has been studied is myofascial syndrome. Results of Ketenci et al. 2009 study have shown that pain severity measured with VAS significantly improved after the first day in the mono-therapy groups (injections and ointment) and after the third day in all groups. The conclusion was that thiocolchicoside can be used in the treatment of myofascial pain syndrome (Ketenci et al. 2009).

The present clinical follow-up is to evaluate the effect of thiocolchicoside 4 mg tablets on clinical manifestations in patients with fibromyalgia as an off-label short-term symptomatic treatment for pain and muscle hypertonicity reduction. We selected only patients with primary fibromyalgia so that we could observe the actual effect of thiocolchicoside administration. Another aim is to observe how its application affects the patient's quality of life.

## Materials and methods

A prospective follow-up observation in ambulatory patients with fibromyalgia, performed in the Clinic of Rheumatology of the University Hospital "St. Ivan Rilski," Sofia, in the period April 2022–October 2022, is presented.

Eighteen patients with primary FM were included in the clinical follow-up: all women, with a mean age of ± 54.38 years, min. 40 years, max. 79 years. The age of onset of FM was ± 49.63 years. The duration of FM symptoms was ± 4.81 years. There is no collected record of previous treatment for fibromyalgia. Also, there is no track record of other concomitant diseases, but serious rheumatic, malignant, and infectious diseases were excluded.

The distribution of patients, according to the etiological factor of FM onset, is presented in Fig. 2.

In essence, unemployment exerts psychological stress and can be classified under the other indicator of psychological strain. However, it is more appropriate to single it out as a separate contributor to the onset of fibromyalgia, as no data is collected as to whether the symptoms are a cause of job loss or vice versa.

The diagnosis was done according to the 2016 ACR criteria and was established for the first time in

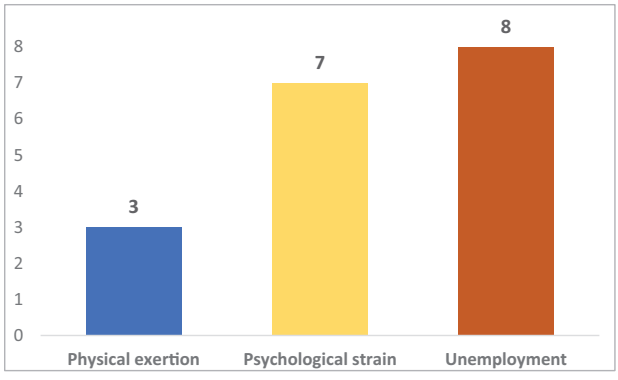


**Figure 2.** The distribution of patients according to the etiological factor of the occurrence of FM.

the included ambulatory patients. The observation endpoints were chosen to be the difference in the number of tender points, pain threshold, fatigue, and quality of life.

The multiple tender points, a common characteristic of fibromyalgia, are essential when using "mild or greater" tenderness as the endpoint. A tender spot is found during palpation, with or without pain (trigger point), and at least three of the following symptoms: muscle stiffness, limited range of motion, pain worsening with stress, and palpation of a taut band or nodule.

The pain threshold measurement with dolorimetry is the only accurate criterion for assessing chronic pain. The evaluation is conducted using the Fisher dolorimeter. The pressure is exercised at a speed of 1 kg/cm$^2$/sec. The patient notes the time the pressure grows into a feeling of pain.

Fatigue was assessed on a Fatigue Severity Scale (FSS) with questions related to changes in physical activity and social function that had to be answered by the patients using a score range from 0—without fatigue—to 8 points—maximum evaluation of fatigue (Goldenberg et al. 1990; Yazici et al. 2003; Wolfe et al. 2016).

To evaluate the efficacy of off-label thiocolchicoside use, the selected endpoint is quality of life. Assessment of fibromyalgia impact on patient's life based on the Fibromyalgia Impact Questionnaire (FIQ)—physical, social, and general parts. It includes self-report questions and measures physical functioning, work status—missed days of work, job difficulty, depression, anxiety, pain, stiffness, fatigue, and well-being over the past week. The developed questionnaire was an attempt to capture the total spectrum of problems related to the nature and management of fibromyalgia (FM). The 2009 version consists of 21 items across the following 3 domains: Function—9 questions, Overall Impact—2 questions, Other Symptoms—10 questions (Burckhardt et al. 1991).

Fibromyalgia is an off-label use for the monitored myorelaxant thiocolchicoside (Tiyozid®). Its primary indication is as an adjuvant treatment of painful muscle contractures in acute back pathology in adults and adolescents aged 16 years and older. The medication is selected to reduce muscle hypertonicity as its primary mode of action. As mentioned above, we aim to achieve a good analgesic effect and decrease pain intensity in patients by reducing the formation of myogelosis at the trigger points in the tender points and breaking the vicious cycle of spasm-pain-spasm.

## Methods

This clinical follow-up is performed in two visits: on the first day when the patient is diagnosed with primary fibromyalgia and on the forty-first (41$^{st}$) day after initiating treatment with thiocolchicoside (Tiyozid®).

This observational study has the following methods for the evaluation of the results:

1. Assessment of the number of painful points with a dolorimeter before treatment (first day) and on the 41$^{st}$ day after treatment.
2. Measurement of pain threshold at 18 pain points before treatment and on the 41$^{st}$ day after treatment.
3. Assessment of fatigue by FSS scale.
4. Completion and assessment of a questionnaire on the impact of fibromyalgia on the patient's activities (FIQ)—physical and social part, general symptoms—before treatment and on the 41$^{st}$ day after treatment.

Because FM is a chronic condition, it was estimated that good clinical impact with thiocolchicoside would be achieved if the therapy's duration covered two consecutive months. Thiocolchicoside (Tiyozid®) tablets are administered 2 times x 4 mg daily for 10 days, with a break of 20 days, and a new treatment course of 10 days.

Clinical safety is assessed according to spontaneously reported adverse effects.

## Statistical methods

Data was processed with the statistical package SPSS 16.0 for Windows. For all comparisons, $p < 0.05$ was chosen as the significance level and quantifies the evidence against a null hypothesis. The results of quantitative variables are presented as arithmetic average ± SD. The non-parametric Kolmogorov-Smirnov test was used to determine the type of distribution. Parametric methods such as Student's t-test and analysis of variance were used when the distribution was correct. In case of incorrect distribution or homogeneity variables, non-parametric methods were used: the Mann-Whitney test, Kruskal-Wallis test, and chi-squared test.

# Results

A total of 18 ambulatory patients with primary fibromyalgia enrolled in this clinical follow-up. No patients dropped out, and all completed it. There is no data for spontaneously reported adverse effects.

## Results of assessment of the number of tender points on the first and 41$^{st}$ day of treatment

The mean number of tender points is an important indicator for diagnosis of fibromyalgia. It can be used in medical practice to monitor the effect of the initiated clinical approach in the treatment of FM.

All patients included in this clinical follow-up with primary fibromyalgia had more than 11 tender points. The average number of pain points before treatment initiation is 15.4 ± 1.9. After the treatment, a statistical reduction in the mean number of pain points is observed in the whole group—13.17 ± 1.5 (Fig. 3).

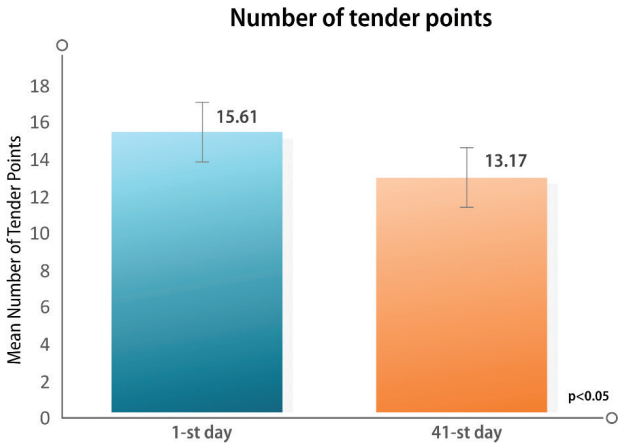


**Figure 3.** Assessment of the number of tender points. P < 0.05, a statistically significant difference in the mean arithmetic values of the number of pain points before and on the 41st day after thiocolchicoside treatment.

## The result of the change in pain threshold measured with a dolorimeter on the first and 41st day of treatment

Usually, the people with active trigger points had much lower pain thresholds than healthy individuals. The increase in pain threshold is another important and precise indicator to monitor the effect of the initiated clinical approach in the treatment of FM.

In this follow-up, an increase in pain threshold after thiocolchicoside treatment is observed in all patients (from 2.37 ± 0.4 to 2.58 ± 0.3, p > 0.05, non-significant) (Fig. 4).

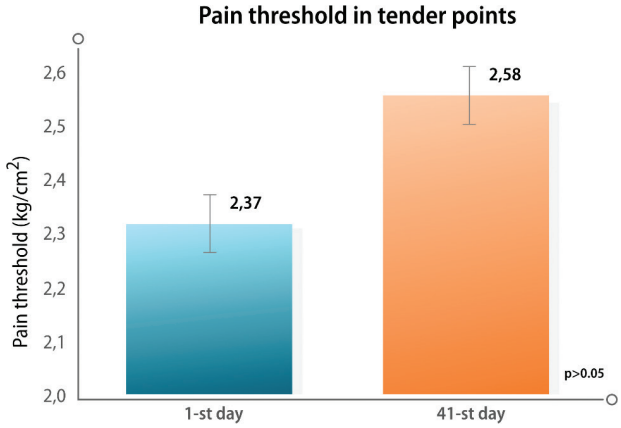


**Figure 4.** Pain threshold in tender points. P > 0.05, a non-statistically significant difference in the mean values of pain threshold before and on the 41st day after thiocolchicoside treatment.

## Results of chronic fatigue assessment by the fatigue severity scale

On the clinical indicator of chronic fatigue on the FSS scale, the mean score before treatment is 7.1 ± 0.8 points and 3.5 ± 1.3 points after treatment. This difference shows a 51% reduction in fatigue, which is in favor of thiocolchicoside (Fig. 5).

It is good to mention here that by SmPC one of the common adverse effects of thiocolchicoside is drowsiness. In theory, this could be attributed to its antagonism with $GABA_A$ receptors (Carta M 2006). Other studies with thiocolchicoside confirm fewer cases of drowsiness (Aksoy et al. 2002; Ketenci et al. 2009; Umarkar 2011).

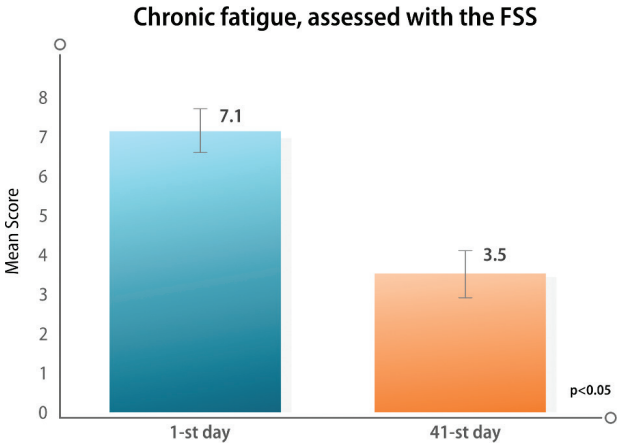


**Figure 5.** Assessment of chronic fatigue. P < 0.05, a statistically significant difference in the mean arithmetic scores before and on the 41st day after thiocolchicoside treatment.

## Results of the evaluation of a questionnaire on the impact of fibromyalgia on the patient's activities: FIQ—general part

According to the endpoint quality of life, there was a significant improvement between the first and 41st day of treatment with thiocolchicoside. The mean arithmetic score was reduced from 37.5 ± 11 points to 28 ± 8 points (p < 0.05) (Fig. 6). This indicates that the thiocolchicoside intervention is effective in improving the participants' fibromyalgia symptoms and decreasing the impact of FM on participants.

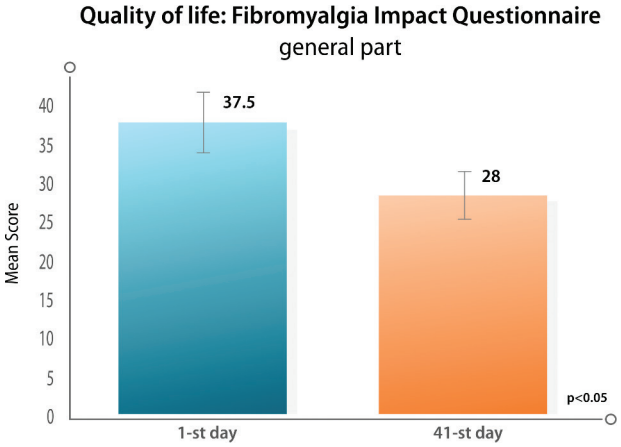


**Figure 6.** Quality of life evaluation with the Fibromyalgia Impact Questionnaire (FIQ)—general section. P < 0.05, a statistically significant difference in the mean arithmetic scores on the first and 41st day of treatment with thiocolchicoside.

## Discussion

This clinical observation evaluates how the short-term application of thiocolchicoside may affect the clinical improvement and quality of life of patients with fibromyalgia (FM), as it is a chronic musculoskeletal disease. Fibromyalgia (FM) occurs in 5–6% of patients in primary care clinics and 10%–20% of rheumatology outpatients (Goldenberg et al. 1990; Wolfe et al. 1995).

The clinical manifestation of fibromyalgia (FM) results from complex mechanisms of central nervous and neuroendocrine regulation that lead to chronic musculoskeletal pain (psychogenic rheumatism, soft tissue rheumatism). Fibromyalgia pain can have a serious impact on the quality of life, making even normal daily tasks difficult. Katz et al. (2021) found that patients with FM have severely impaired intramuscular pressure. Also, it was observed that hypertonicity directly correlates with pain symptomatology and limited range of motion. Another conclusion of Katz et al. (2021) is that from a therapeutic point of view, reducing muscle hypertonicity can significantly change the clinical condition. This is a reason why physicians should consider the addition of myorelaxants to fibromyalgia therapy. The clinical presentation of fibromyalgia is not limited to pain and increased muscle tone (muscle hypertonicity). It is even more complex, as patients complain of fatigue, sleep disturbances, depression, anxiety, and congestion, necessitating a comprehensive approach to initiating therapy.

Improvements from baseline were seen in the present clinical observation with statistically significant differences after treatment with thiocolchicoside according to the main endpoints: number of pain points ($p < 0.05$) and pain threshold ($p > 0.05$).

According to Yazici et al. (2003), fatigue is the next debilitating symptom and impairs the quality of life of patients with FM. There is a close association between chronic pain and fatigue in patients with fibromyalgia. Krupp et al. (1989) note that the quality of life of patients with FM related to pain and accompanying clinical complaints is extremely low.

Based on the current follow-up data concerning chronic fatigue as assessed by the FSS scale, there is a statistically significant difference in the mean arithmetic values on the 1st and 41st day of treatment with thiocolchicoside. According to the quality-of-life criteria, the data from the current follow-up indicates that the patient's quality of life has improved after using short-term thiocolchicoside therapy.

In addition, for successful clinical outcomes, patients need special individual education and good communication about their FM disease and treatment to maintain a good quality of life. It is also associated with an increase in pain threshold due to pharmacological or non-pharmacological treatment. Therefore, primary care within the family is important for the success of the treatment. In order to achieve good therapeutic outcomes in FM, physicians should be more assertive about patients' adherence to therapy and have regular check-ups at least once a month. Another important part of the clinical approach is that the physicians should take a detailed patient history and go into depth about the encapsulated problems. This makes a huge difference in the trust of the treatment and its outcome. Comprehensive treatment of patients with FM aims at clinical improvement and increased quality of life.

## Conclusion

Fibromyalgia syndrome is characterized by chronic pain and an elevated number of pain-sensitive trigger points in affected individuals. Furthermore, reducing muscle hypertonicity at trigger points can significantly ameliorate the patient's condition. Pharmacological management should be considered a co-adjuvant to non-pharmacological therapy and should be guided by the patient's symptoms.

Though further large follow-up studies in clinical practice are needed, these findings suggest that adding thiocolchicoside (Tiyozid®) to the clinical approach in fibromyalgia patients could result in a reduction in pain intensity. The thiocolchicoside treatment also reflects on the increase of pain threshold at the trigger points and reduces the number of painful points. From the analysis of other endpoints, thiocolchicoside diminishes the degree of chronic fatigue in patients with primary fibromyalgia, has an overall positive effect on everyday activities, and improves the quality of life.

We acknowledge several limitations in this follow-up: lack of a placebo group, a small number of patients, only patients with primary fibromyalgia, no data for basic characteristics (weight, education degree, living area), no history data for some treatment before diagnosis, off-label use of thiocolchicoside in fibromyalgia, the duration of the thiocolchicoside administration, lack of a therapy follow-up diary, and precise observation of adverse effects. The main limitation is the small number of patients with primary fibromyalgia. This main reason in clinical practice is common and usually is due to reduced patient adherence to therapy and feedback (about the effectiveness and adverse effects). A large-scale quantitative follow-up with patients with fibromyalgia and a placebo group could present more conclusive results about the use of the central-acting myorelaxant thiocolchicoside in FM.

## Additional information

### Conflict of interest

Clinical follow-up was commissioned by Nobel Pharma Bulgaria, for the company's clinical data needs. Valentina Reshkova and Simeon Monov declare no conflicts of interest in the preparation of the presented report. Alexander Mandadjiev is an employee of Nobel Pharma Bulgaria in the position of Medical Advisor.

### Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.
The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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This work was supported by Nobel Pharma Bulgaria.

### Author contributions
All authors have contributed equally.

### Data availability
All of the data that support the findings of this study are available in the main text.

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