

# Sulfosin, a centennial drug between therapy and punishment

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## ABSTRACT

Since antiquity, fever has been known to improve the course of a mental illness. Based on this evidence, Julius Wagner von Jauregg successfully used malaria inoculation to treat patients with general paralysis of the insane in 1917, a procedure that was soon expanded to the treatment of other forms of neurosyphilis and mental illnesses. Given the complexity and undesirable effects of the method, other less risky therapies were sought. One of the simplest and most effective drugs was sulfosin, a preparation of sulphur dissolved in olive oil introduced by Knud Schroeder in 1924. In the late 1920s and the 1930s, the drug was used in several countries, including Spain, for the treatment of neurosyphilis and particularly for schizophrenia and other mental illnesses, until it was replaced by other more effective methods, such as shock therapies and, in the case of neurosyphilis, penicillin. However, the Soviet Union continued to use it as a treatment and also for repressive purposes, due to the pain caused by its intramuscular administration, and the drug became a symbol of punitive psychiatry. Though only sporadically, it continues to be used in Russia and other former Soviet republics.

## KEYWORDS

Sulfosin, Knud Schroeder, pyretotherapy, neurosyphilis, schizophrenia, Soviet punitive psychiatry

## Introduction

It has been nearly a hundred years since the development of sulfosin, a drug used in pyretotherapy and introduced in psychiatric practice by Knud Schroeder in February 1924, and that is still used today, though in very restricted circumstances.

The introduction of malariotherapy by Julius Wagner von Jauregg in 1917 was a key event in the history of psychiatry, breaking with the dominant therapeutic nihilism at the time. The recent literature on pyretotherapy is limited. Pyretotherapy consists of provoking fever by the inoculation of malaria or the administration of

various alternative therapeutic agents (proteins, bacteria, chemical compounds) with a better safety profile. These procedures were used for the treatment of general paralysis of the insane, a previously incurable disease, and other mental illnesses, including schizophrenia; this led to optimism in the 1920s and 1930s and paved the way for the development of new, more effective therapies.

Sulfosin was one of the safest and most straightforward pyretotherapy agents, and was widely used in several countries including Spain in the late 1920s and the first half of the 1930s, progressively falling into disuse. However, sulfosin continued to be used in the USSR,

where it became a symbol of punitive psychiatry between the 1960s and 1980s.

This study analyses the history of sulfosin and its use to treat various diseases worldwide, with greater focus on the Spanish setting. I also analyse in detail its use in Soviet Russia, considering its idiosyncrasy, for the purposes of both therapy and repression.

### Material and methods

A systematic review was conducted of the international literature, including Russian articles, on pyrethotherapy in general and the use of sulfosin in particular for the treatment of neurosyphilis, schizophrenia, and other functional mental illnesses and neurological diseases. Special attention is paid to the scientist who discovered the drug, Knud Schroeder; the clinicopharmacological and pathophysiological characteristics of sulfosin; and its use in different countries, with special reference to Spain and the Soviet Union, due to the special characteristics of its use in the latter case.

### Development

#### Background

Since antiquity, fever and infectious agents have been known to present beneficial effects for a wide range of nervous diseases. Hippocrates mentioned the effectiveness of malaria in epilepsy and Galen cited a case of melancholy cured as a result of quartan fever.<sup>1</sup> Likewise, in the 16th century, Paracelsus and Ruiz de Isla, who described the positive impact of fever on the condition later known as neurosyphilis, also reported this benefit.<sup>2</sup> In the 17th and 18th centuries, Sydenham and Boerhaave knew of the effect of fever on insanity, which was also described in the 19th century by Pinel, Esquirol, Briquet, Janet, Mingazzini, Gordon, and Maudsley, among others.<sup>1,3,4</sup>

In 1846, Vasily Sabler, based on his observations of patients with general paralysis of the insane, reported that intermittent fever may be beneficial in the treatment of some mental illnesses. Influenced by Sabler, Alexander Rosenblum (1826-1903), director of the psychiatry department in Odessa, was the first to induce an infectious disease in patients with mental illnesses, observing the curative effects of malaria, typhoid fever, and recurrent fever in psychosis; he published his findings in 1876. He studied 22 patients with attacks of recurrent fever; of these, 11 recovered and three presented partial

improvements. While Rosenblum did not explicitly mention that he triggered the fever, it seems to have been the case, as suggested by Mochutkovsky, head of the infectious diseases department at Odessa Hospital, who referred to recurrent fever episodes induced by inoculations.<sup>1,5</sup> In 1943, Zakon and Neymann published an English translation of Rosenblum's article.<sup>6</sup> In 1876, Raggi from Bologna also recommended inoculating malaria in patients with mental illness.<sup>7</sup>

#### Malariotherapy

In 1883, the Viennese psychiatrist Julius Wagner von Jauregg (1857-1940) observed how a patient's mental illness improved after erysipelas. In an article published in 1887, he reviewed the beneficial effects of typhoid fever, intermittent fever, erysipelas, and anthrax in patients with mental illnesses, and suggested their use as possible treatments for psychosis; however, he was unsuccessful with inoculations of streptococci, tuberculin, and similar initiatives. In 1917, he administered injections of *Plasmodium vivax* to nine patients with general paralysis of the insane, provoking tertian fever; after several febrile seizures, he administered quinine to resolve the malarial infection. After this procedure, six patients presented total or partial remission of their mental illness. Von Jauregg had already performed 120 procedures by 1921 and more than 1000 by 1925, with 60% of patients achieving some type of remission. Complete remission was observed in 30% of the patients and partial remission in another 30%. The technique spread to other countries and was used in tens of thousands of patients with neurosyphilis, combined with arsenic and bismuth therapy.<sup>1,8</sup>

The application of malariotherapy to treat general paralysis of the insane represented one of the great achievements of the medical science of that time, but also presented disadvantages. The technique was complicated and required the infection to remain active in the human reservoir, which was only possible in large asylums. Furthermore, some weakened patients died, and there were some contraindications for use of the technique.<sup>9</sup>

This procedure was also used to treat schizophrenia and other mental illnesses, but its benefits did not outweigh the risks of applying it to these patients, who presented a good vital prognosis and whose response to treatment was less evident than in patients with neurosyphilis.<sup>10</sup>

### Other forms of pyretotherapy

Pyretotherapy developed rapidly as a result of the success with malariotherapy in treating the general paralysis of the insane. Although such other germs as those causing recurrent fever and sodoku were also used, alternatives were sought that did not cause infection in patients. Such microbial agents as tuberculin (discovered by Koch), chancre vaccine (Dmelcos), antityphus and smallpox vaccines, active saprophytes (saproviton), non-pathogenic *Escherichia coli* proteins (pyrifer), and lipopolysaccharides from *Pseudomonas aeruginosa* and *Salmonella typhi* (pirogenal).<sup>3,11</sup> The latter compound was developed in the 1950s by Moscow's Gamaleya Institute directed by Juan Planelles.<sup>12</sup> Such organic products as milk and its derivatives, phlogetan, and sodium nucleinate were also administered by intramuscular injection. Chemical agents administered included sulfosin; turpentine essence administered subcutaneously, provoking fixation abscess; and metals including colloidal silver injected intravenously (electrargol). Furthermore, such physical methods as hot baths and long-wave, short Hertzian wave, hot air, and infra-red diathermy were also used.<sup>3,11,13</sup>

In the second half of the 1930s, pyretotherapy began to lose ground in the treatment of functional psychoses, in favour of more modern and effective methods such as cardiazole shock therapy, electroconvulsive therapy, and insulin coma, which in turn gave way to modern psychoactive drugs in the 1950s.<sup>14</sup> Neurosyphilis nearly disappeared in the 1940s thanks to the discovery of penicillin.

### The introduction of sulfosin

The Dane Knud Schroeder (1877-1955) was the first to use sulfosin to treat mental illness. He was aware of the complexities of malariotherapy for general paralysis of the insane, a condition with which he had personal experience.<sup>15</sup> In February 1924, he administered intramuscular sulphur oil to a patient with taboparesis, which caused high fever followed by a surprising improvement. He made the preparation himself by crushing sulphur into olive oil sterilised by dry heat, in a 1% solution.<sup>16</sup> At that time, he had already injected sulphur oil in patients with joint disorders, based on the experience of Meyer-Bisch and Basch on arthritis deformans, published in 1921.<sup>17,18</sup>

At the 13th Northern Congress of Internal Medicine, held in Copenhagen in June 1927, he presented his preliminary findings on the therapeutic effects in general paralysis of the insane of intramuscular administration of a 1% suspension of sulphur in olive oil (later known as sulfosin), a preparation that increased body temperature to 39-40°C. He indicated that it was similar to treatment with malaria inoculation, but with fewer adverse effects. It may be used in patients who did not respond to malaria infection therapy or presenting contraindications to the treatment, or in cases in which the procedure could not be performed for technical reasons.<sup>2,19</sup> At the congress, he presented seven cases of paralytic dementia treated with sulfosin, with five presenting remission or a significant improvement, and encouraged his colleagues to try the technique.<sup>15,18</sup> In 1929, he published new findings in *The Lancet*,<sup>19</sup> which published several articles on the topic in the following years.

Knud Schroeder was born in Copenhagen and graduated in medicine in 1903. He worked at hospitals in his home town and the university laboratory. From 1912, he worked as physician-in-chief at the Odense county and city hospital. He held several executive positions at the Danish Medical Society and was a member of organisations created to fight tuberculosis and control arthritis as well as the German Association of Psychiatry and the French Union Thérapeutique.<sup>15,20</sup>

In 1925, the Palestinian physician Djamil Tutunji recommended the use of intramuscular injections of colloidal sulphur (Sulfoïdol Robin) in paralytic dementia, a treatment similar to malariotherapy but not involving infection. Malaria was endemic in his region, whereas syphilis was infrequent, and therefore he encouraged colleagues from other countries to use the technique.<sup>21</sup>

### Sulfosin preparations

Sulfosin was prepared by Schroeder and manufactured from 1927 by Lovens Kemiske Fabrik in Copenhagen in 1-, 5-, and 10-cc ampoules under the name Sulfosin Leo.<sup>18</sup> The 1% solution of sulphur in olive oil crystallised when cooling and had to be reheated before use.<sup>22</sup> The ampoules contained preparations of colloidal sulphur analogous to sulfosin, for intramuscular injection: Sulfoïdol Robin<sup>21</sup> and Thi-lip Aguetant<sup>11</sup> in France, and Colsul (Crookes Laboratories) and Collosol Sulphur (British Colloids) in England.<sup>23</sup> Several years later, new formulations were developed, including Neosulfosin<sup>22</sup> and Anaesthesulf,<sup>24</sup> both containing sulfosin combined with benzocaine to

mitigate pain. Another presentation was Sulfosin fortior, including sulphur at 2%, which was helpful for reducing the injection volume when high doses were needed.<sup>2,22</sup> The effect of raising the body temperature was similar in all preparations.<sup>23,25,26</sup>

In the USSR and former Soviet republics, sulfosin has been used under the name Sulfozin or Sulfozinum; sulphur was generally dissolved in peach, olive, or sunflower oil, with 0.37%, 1%, and 2% preparations that are currently prepared at the hospital. If the drug was not going to be used for disciplinary or repressive reasons, 0.5-2 mL of 2% novocaine was injected prior to sulfosin.<sup>2,27</sup>

#### Means of sulfosin administration

Schroeder used deep intramuscular injections of sulfosin at the subperiosteal level on the lateral side of the femur, between the middle and upper third of the thigh. Maximum temperature was achieved at approximately 12 hours after the injection, with a brief peak followed by a slow decrease over 24-48 hours. Treatment started with a dose of 0.5-1 cm<sup>3</sup>, gradually increased by 1 cm<sup>3</sup> increments until eventually reaching 10-12 cm<sup>3</sup>. The following dose was administered when fever has resolved, with an approximate frequency of two to three injections per week. A series of 10 injections was administered, and if there was no clinical improvement, this series was repeated after two weeks, with no more than three series generally administered. Injections caused hypersensitivity and severe pain at the injection site, as well as antalgic limitation of the range of movement of the lower limbs for two to three days.<sup>19</sup> Later, sulfosin was administered by deep intragluteal injection, which was less painful,<sup>22,28,29</sup> and occasionally below the scapulae.<sup>2</sup> It was preferably administered early in the morning or in the mid-afternoon in order not to interfere with nocturnal sleep (Figure 2).<sup>25,30,31</sup>

A temperature above 39°C (102°F) was achieved in almost all patients, with more than half reaching temperatures above 40°C (104°F).<sup>32</sup> Patients rarely reported chills. The most surprising finding was leukocytosis, with cell counts of 20 000-35 000 and 80%-90% polymorphonuclear cells. Patients presented a slight decrease in arterial blood pressure, asthenia, and anorexia, and lost between four and seven kilograms of weight over a course of 10 injections. Final doses of 8-10 cm<sup>3</sup> could destroy a large amount of muscle. If more than one series of treatment was administered, patients

may present fibrosis, scarring, and residual symptoms of muscle function loss.<sup>33</sup>

#### Sulfosin in neurosyphilis

Sulfosin was indicated for general paralysis of the insane and other types of neurosyphilis, congenital syphilis, and serum-resistant syphilis.<sup>34</sup> Schroeder recommended treating syphilis with sulfosin, even in children and infants, pregnant women, elderly people, and patients with inactive pulmonary tuberculosis.<sup>19</sup> Kallmann used it in all cases of general paralysis of the insane in patients older than 60 years and in those presenting obesity, physical decline, taboparesis, and tuberculosis.<sup>35</sup>

Schroeder considered treatment with sulfosin to be equivalent to malariotherapy for general paralysis of the insane, but without its dangerous effects. Its main disadvantage was the intense local pain. It could be used in centres with few patients that were not equipped to store strains of *Plasmodium vivax*, a malaria pathogen that also caused a disease with potential complications, including mortality. Patients were also treated with arsenic and bismuth.<sup>9,32,36</sup>

Schroeder treated 14 cases of general paralysis of the insane with sulfosin, all of whom reached body temperatures above 39°C. The response included remission and hospital discharge in 8 patients, 5 of whom seemed to have been cured. He also treated six patients with cerebrospinal syphilis, with resolution in three, and eight patients with tabes dorsalis who also presented remission; optic atrophy also remitted in another patient with tabes.<sup>9</sup>

Marcuse and Kallmann treated 32 patients, with a remission rate of 59%, and Jacobsen and Smith treated another 27, with a 32% remission rate. Warstadt obtained poorer results in a series of 11 cases, with five not responding to malariotherapy and only two presenting remission.<sup>9</sup> In another publication by Franz Kallmann, 32 of the 402 patients with general paralysis of the insane at the Anstalt Herzberge in Berlin were treated with sulfosin, achieving complete remission in six and partial remission in seven (43%).<sup>35</sup>

In England, Laptain used sulfosin to treat 12 patients with advanced general paralysis of the insane. The disease remitted in two patients, who were discharged from hospital, and nine showed some degree of improvement.<sup>37</sup> However, in 1930, Patterson and Switzer treated 19 patients with general paralysis of the insane

but did not achieve the high temperatures obtained by Schroeder, or the same clinical outcomes.<sup>38</sup>

In the United States, Kuhns and Wilgus used sulfosin between 1928 and 1929 to treat 100 patients with paresis, achieving an improvement in 58%; Read treated another 14 patients, reporting a pronounced improvement in 11, with complete remission in eight.<sup>39</sup>

In 1928, the Japanese psychiatrist Takase Kiyoshi studied the intramuscular administration of sulphur in 74 cases of general paralysis of the insane and tabes dorsalis, finding it to be as effective as malariotherapy.<sup>20</sup>

Winkler treated five cases of tabetic optic atrophy, with three showing improvement, whereas none of the patients treated by Stiefler showed an improvement of their optic atrophy, although tabetic symptoms improved in all cases.<sup>19</sup> In 1932, Schroeder published four cases of syphilitic parenchymatous keratitis, and Larsen reported another 17 between 1933 and 1939, all treated successfully.<sup>22</sup>

#### Sulfosin in functional psychoses

From the late 1920s to the mid-1930s, pyreotherapy was widely used in non-syphilitic psychoses with such agents as sulfosin, which were less dangerous and easier to use than malariotherapy. Results were generally more modest than in neurosyphilis.

Among his first patients, Schroeder used sulfosin to treat six patients with schizophrenia; three presented remission and two showed a partial improvement.<sup>40</sup> Loberg used the drug in 135 patients with schizophrenia, 62 of whom showed remission, though this was only permanent in 12. Marcuse and Kallmann used it in 46 patients with schizophrenia, 16 showing an improvement and four returning to normal life. Salinger treated another 16 patients, with four presenting remission.<sup>41</sup> Langelüdekke used the drug to treat 35 patients with schizophrenia, with 51.4% improving. In a control group of 60 patients with similar characteristics but who received the same care but were not administered sulfosin, 23.3% showed improvements.<sup>26</sup>

In Great Britain, Collingwood Fenwick used sulfosin to treat 30 young men with dementia praecox. Eight presented complete remission and seven showed significant improvements.<sup>30</sup> McCartan treated 23 cases of dementia praecox with sulfosin, achieving significant improvements in four and moderate improvements in three.<sup>42</sup> Minski used sulfosin in 20 patients with

schizophrenia, with two fully recovering, one showing significant improvement, and four presenting transient remission.<sup>41</sup> McCowan and Northcote used sulfosin and collosol to treat 45 cases of functional psychosis. Twenty-one of these patients had advanced schizophrenia, with five showing a slight improvement and one fully recovering. Of the 13 patients with schizophrenia of short progression, six improved, with one presenting complete remission. All six patients with manic-depressive psychosis improved. These British authors were convinced that the benefit was mainly psychological, as the pain and discomfort caused by the drug and nursing attention interrupted their fantasy life.<sup>23</sup> Macmillan and Wyllie treated 21 cases of persistent psychosis with sulfosin, including seven patients with moderate improvement and one patient with melancholy who presented a full recovery. They considered this drug to be the ideal agent to induce fever, although with little clinical benefit.<sup>43</sup>

In France, Henri Claude and his group established in 1933 a protocol for pyreotherapy with combined administration of sulphur oil and gold salts to treat dementia praecox. They acknowledged the dual difficulty of the diagnostic uncertainty and the disconcerting course of the disease. Younger patients with confusional psychoses of recent onset responded better and faster to treatment. In 1935, Claude and Dublineau presented 34 cases of dementia praecox treated with combination therapy with sulfosin and gold salts; 13 showed complete remission and seven partial or transient remission.<sup>44</sup> In 1934, Donnadieu and Lôo used sulfosin to treat 10 patients with dementia praecox, achieving complete remission in three. Acute forms emerging in patients living an almost normal life were simpler to treat.<sup>29</sup> Trillot, after an initial experience using sulfosin to treat four women with schizophrenia (two of whom fully recovered), presented 19 more patients, reporting that eight showed significant improvement and three transient improvement. He also recommended this treatment in the early stages of psychosis.<sup>45</sup>

In Italy, Ceroni used sulphur to treat 50 patients with different mental illnesses. Outcomes were particularly good in the group with manic depression, with less promising outcomes in the group of patients with schizophrenia. The treatment was also unsuccessful in patients with epilepsy.<sup>46</sup>

In countries where malaria was endemic, such as India and Palestine, many patients showed resistance to the

infection, and very few patients with syphilis presented nervous system involvement. Malariotherapy in these patients had little effect<sup>13,20,21</sup>; this was also observed in some areas of Spain, for instance in the provinces of Cáceres and Seville.<sup>28</sup> In August 1930, Jal Dhunjibhoy, Medical Superintendent at Ranchi Mental Hospital in India, trialled sulfosin treatment in 100 patients with psychosis using the method described by Schroeder, with whom he maintained correspondence. Dhunjibhoy, a member of the Parsi community educated in Europe, personally prepared a 1% solution of sulphur in olive oil, which he used to treat mental illnesses refractory to other treatments. He reported no cases of neurosyphilis. Of the first 100 patients he treated over 18 months, 37 presented manic depression, 44 schizophrenia, and eight epileptic psychosis. Overall, 13 cases remitted and 39 improved, although 18 of these relapsed. No epileptic patient showed any improvement.<sup>31</sup> By 1933, he had trialled the treatment in 215 patients, and in more than 500 in 1937, using it routinely in new patients admitted with psychosis or psychoneurosis.<sup>20</sup>

Pyretotherapy in general had little positive effect on schizophrenia. In 1932, Gino Nutini gathered 1795 cases of dementia praecox treated with the different types of pyretotherapy, observing recovery in 10% and improvements in 30%.<sup>47</sup> In 1934, Jørgen Ravn stressed the errors made in the diagnosis of schizophrenia, the spontaneous recoveries, and the tendency of these patients to respond to treatment by suggestion. He published a table including the clinical progression of 366 previously published cases treated with sulfosin, and another including 543 patients who received no treatment. The percentages of patients showing remission and recovery were similar in both tables, and Ravn concluded that all the benefits of sulfosin were the result of suggestion. Furthermore, no clinical trial could be performed, as no control group could be included.<sup>48</sup>

#### Sulfosin in Spain

Malariotherapy for general paralysis of the insane was introduced in Spain in 1924 by Rodríguez Lafora and in 1927 by Vallejo-Nágera, who was its main supporter.<sup>14</sup> Although it was also used to treat functional psychoses, its side effects and possible mortality led to the use of less complicated procedures such as the antityphus and smallpox vaccines, pyrifer, saprovan, fixation abscess caused by turpentine, and sulfosin, as well as other physical methods.<sup>7,49</sup>

Mendiguchia, Martín-Vegué, and Fernández Méndez, of the Leganés insane asylum, published in August 1930 an article on eight patients treated with sulfosin for four and six months. The six patients with dementia praecox showed partial improvements, whereas in the two patients with advanced general paralysis of the insane, the treatment only had a sedative effect.<sup>36</sup> In 1931, Enrique Fernández Sanz, the director of the asylum, spoke at the Spanish Royal Academy of Medicine about sulphur therapy in psychiatry. He proposed that it should be used in paralytic dementia and schizophrenia, aiming to replace malariotherapy. In his opinion, the intensity of its action and certain other characteristics made it stand out from similar drugs. He had treated four patients with general paralysis of the insane with sulfosin, with one showing remission that lasted seven months. From early January to October 1930, sulfosin had been administered to 11 patients with schizophrenia, whose clinical symptoms rapidly and significantly changed; patients more or less completely returned to normal life, and four returned to family life.<sup>50</sup> Some of these patients had previously been described in the article by Mendiguchia et al.<sup>36</sup>

In 1931, Rodríguez Arias, Pons Balmes, and Juncosa presented their preliminary experience with sulfosin at the Sant Boi de Llobregat Sanitarium. They showed the records of eight cases (Figure 1) with various mental illnesses, without mentioning the clinical response, and highlighted the advantages of achieving a high and reproducible fever with few undesirable effects.<sup>28</sup> In 1932, Rodríguez Arias and Pons Balmes published a monograph on pyretotherapy in neuropsychiatry. They reported having treated 30 cases of schizophrenia with sulfosin (Figure 2), observing only transient remissions in some patients.<sup>3</sup>

Bordas-Jané, of the mental clinic in Santa Coloma de Gramanet, reported that 43 patients had been treated with sulfosin by 1934. Among nine patients with general paralysis of the insane who also received arsenic and bismuth, two presented complete remission, and another two were able to reintegrate into society. Among the 18 treated patients with schizophrenia, the treatment had limited benefits, with one total and four transient remissions. Six psychoneurotic patients and two post-encephalitic patients responded well, whereas two epileptic patients responded poorly. The best responses were observed in patients in states of agitation.

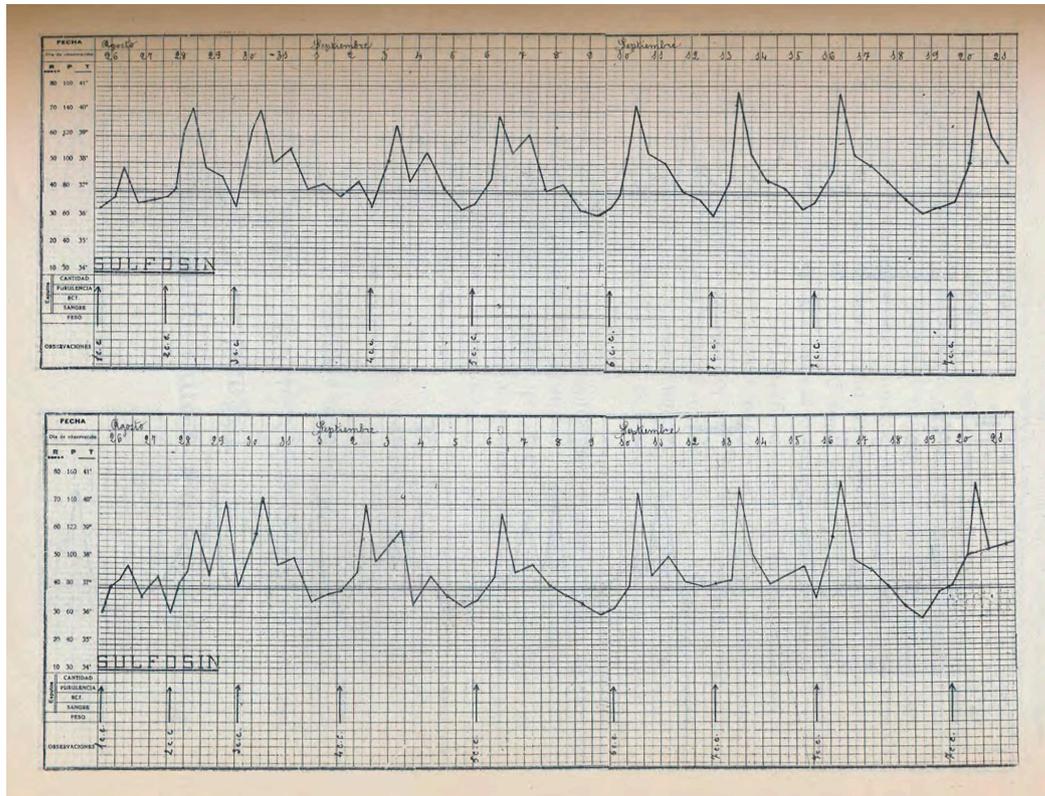


Figure 1. Graphic of temperatures of patients treated with sulfosin at the Sant Boi de Llobregat Sanitarium.<sup>28</sup>

Outcomes with sulfosin were better than those achieved in a similar group of patients treated with turpentine essence.<sup>51</sup>

Of the 178 patients attended during the period 1924-1932 at the Conxo asylum in Santiago de Compostela, 58 received different treatments, of whom 56% presented schizophrenia and 9% manic-depressive psychosis. The most widely used treatment was pyretotherapy with sulfosin, in 24% of patients, followed by fixation abscess in 21% and malariotherapy in 17%.<sup>49</sup> In 1931, José Pérez López-Villamil, interim lecturer at the medical school in Santiago de Compostela and psychiatrist at the Conxo asylum, wrote his doctoral thesis on pyretotherapy using methods other than malaria inoculation in 43 patients with schizophrenia, some of whom were treated with sulfosin. He observed a limited clinical response, with only 13.8% showing improvement.

He concluded that pyretotherapy was of little value for achieving remission. The thesis also included a histological study of the brains of seven rabbits, in which he studied microglial reactions after injection of various pyretotherapy agents.<sup>10,49,52</sup>

In 1934, Jaume Pi-Sunyer studied the physiology of thermal regulation by injecting sulfosin in dogs and rabbits.<sup>53</sup>

In a monograph published in 1940, Ramón Sarró mentioned that, unlike general paralysis of the insane, schizophrenia responded better to such chemical agents as sulfosin than to malariotherapy.<sup>54</sup>

From 1934, pyretotherapy was gradually replaced by new therapies introduced in Spanish psychiatry, including cardiazole shock therapy, insulin coma, and electroconvulsive therapy, as well as penicillin in the



Figure 2. Advertisement for Sulfosin Leo (1932).<sup>3</sup>

case of neurosyphilis.<sup>55</sup> In 1945, sulfosin was still being used in Guipuzcoa.<sup>56</sup>

Sulfosin in the treatment of other nervous system disorders and various other diseases

Schroeder used sulfosin in four patients with post-encephalitic parkinsonism and a patient with probable Parkinson's disease, with improvements in all cases, and very pronounced improvements in four. Verploegh also treated a patient with Parkinson's disease, who presented an extraordinary improvement after four injections of sulfosin. Stiefler used the drug to treat 15 cases of post-encephalitic parkinsonism, observing moderate improvements.<sup>40</sup>

Contradictory results were reported for multiple sclerosis. Schroeder treated three cases, finding no therapeutic effect and also observing overactive bladder at the end of treatment, which was also reported in one of Bichel's patients. However, Stiefler treated 12 patients and obtained promising results.<sup>40</sup> In the case of epilepsy, different series report limited effects.<sup>31,46,51</sup>

In 1938, Schroeder reported that sulfosin had started to be used to treat brucellosis and acute anterior poliomyelitis.<sup>34</sup> The drug was also trialled to treat leprosy, with no clear results.<sup>24</sup>

Sulfosin was also used to treat rheumatoid arthritis and other rheumatic disorders.<sup>17,57</sup>

In 1953, Jiménez Díaz recommended using sulfosin for persistent asthma attacks. He progressively doubled the dose until reaching four to six episodes of fever above 39°C.<sup>58</sup>

In 1955, Eriksson-Lihr of Helsinki used intramuscular sulfosin to treat non-specific desensitisation in patients with allergies, reporting positive results.<sup>59</sup>

#### Action mechanism of pyretotherapy and sulfosin

Mackay injected high doses of sulfosin in rabbits and found local lesions and necrosis. He attributed fever to the release of proteins by the muscle due to the sulphur, or to tissue irritation due to hydrogen sulfide. The injection caused a necrotic reaction, with destruction of the muscle tissue and a pronounced inflammatory reaction. He suggested that the body's response to the sulphur injection was explained by the gradual absorption of proteins and their fragments.<sup>33</sup>

In neurosyphilis, spirochaetes were destroyed by the increase in body temperature and the biological response to the presence of proteins and other non-specific exogenous agents, potentiating the brain's defence mechanisms against the condition.<sup>13</sup>

The increase in body temperature triggered by pyretotherapy has been associated with hyperactivation of the hypothalamic-pituitary-adrenal axis, with release of corticotropin, corticotropin-releasing hormone, and cortisol, which was accompanied by neutrophilic leukocytosis and increased thyroid, adrenal, and sympathetic nervous system function. Prostaglandins, leukotrienes, and inflammatory cytokines are released that activate the thermoregulatory centre of the thalamus, causing fever. It also increases the permeability of vascular and tissue barriers, including the blood-brain barrier, to cells and immune factors, as well as to antibiotics and psychotropic drugs. The treatment affects the balance of neurotransmitters, especially monoamines, gamma-aminobutyric acid, opioids, endocannabinoids, and thermal shock and oxidative stress proteins.<sup>60</sup>

As previously mentioned, the beneficial effect of sulfosin on functional psychoses may be partially or completely psychogenic, with the discomfort and pain caused by the injection and the frequent nursing attention potentially leading to increased connection of the patient with the environment.<sup>23,43</sup>

### Sulfosin in the USSR and the former Soviet republics

After a comparison of several pyretotherapy methods in the USSR, sulfosin (known as Sulfozin or Sulfozinum) was considered from 1934 to be the mildest, safest, and most efficient agent for inducing therapeutic fever. It was used to treat neurosyphilis until the discovery of penicillin, and on a continuous basis to treat classic mental illnesses, such as schizophrenia and other psychoses, depression, hysteria, decompensation in aggressive and explosive psychopaths, and alcohol and drug abuse. It was used for longer in the USSR than in Western countries; as recently as 2002, treatment guidelines still recommended it for treatment-resistant depression.<sup>2</sup> It has also been used in patients presenting resistance to psychotropic drugs, to improve their absorption.<sup>2,61</sup>

In 1941, Smorodinskaya published 150 patients with schizophrenia treated with sulfosin, who presented remission in 16.7% of cases and improvement in 32.1%.<sup>62</sup> Such prestigious psychologists as Gurevich, in 1949, and Gilyarovsky, in 1954, recommended sulfosin as an alternative to malariotherapy in general paralysis of the insane and schizophrenia, even in its sluggish form, as well as in the treatment of other mental illnesses. In 1956, Malkin published a review of several series of schizophrenic patients treated with sulfosin, and reported complete remission in 18.7% and a significant percentage of partial remissions, with better responses in adolescents and young adults.

In 1957, Kameneva considered insulin or sulfosin therapy to be more important than psychoactive drugs in some forms of schizophrenia,<sup>2</sup> despite the recent approval of chlorpromazine (Aminazin), the first antipsychotic drug in the USSR, in 1955.<sup>63</sup> Also in 1957, Detengoff used high initial doses of sulfosin to treat acute schizophrenia-like psychoses, gradually reducing the dose as patients improved, whereas in chronic forms, he started with low doses, which he gradually increased. He also used it to treat sluggish schizophrenia, administering low daily doses that caused no fever but that he believed to have a detoxification effect. The same author continued recommending the treatment in 1969 to alleviate acute psychomotor agitation in patients with schizophrenia, manic states, and agitated depression. A Ukrainian study published in 1995 used sulfosin in 26 schizophrenic patients, reporting positive results. The same year, Platinov recommended moderate doses of antipsychotic drugs associated with glucose-lowering doses of insulin and mild doses of sulfosin.<sup>2</sup>

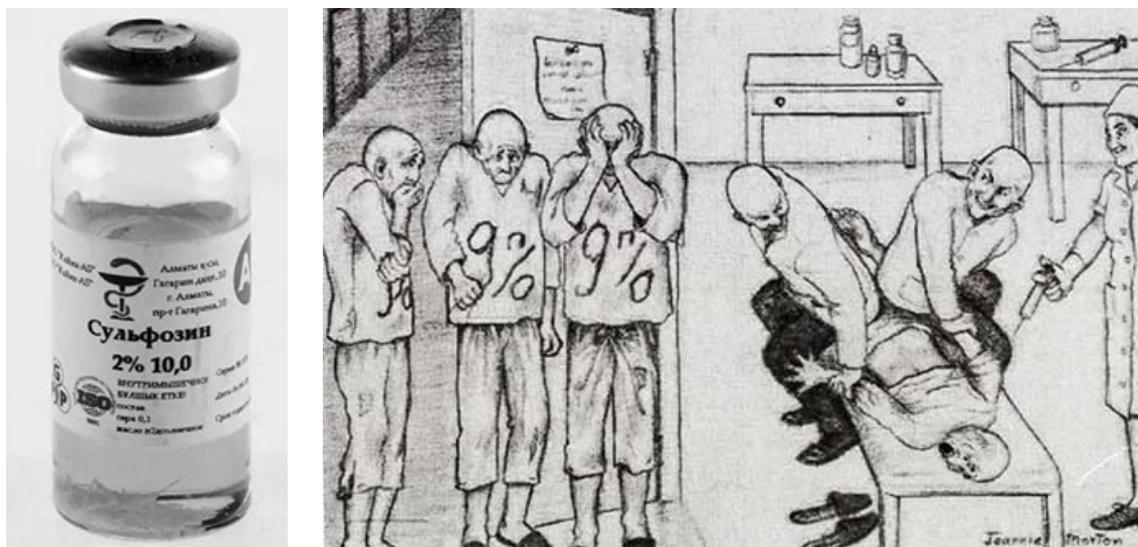
Soviet narcologists used sulfosin to treat patients presenting alcohol abuse or withdrawal syndrome. Wismont reported in 1985 that sulfosin reduces the symptoms of alcohol withdrawal syndrome and alcohol craving, interrupting its excessive consumption. In 2012, Baybabayeva still recommended sulfosin as a treatment for drug addiction, especially in alcohol abuse and abstinence of opioids.<sup>2,60,64</sup>

### Punitive psychiatry

Sulfosin became a symbol of Soviet punitive psychiatry, which took place between the 1960s and 1980s to socially isolate political and religious dissidents, members of ethnic minorities, and other figures who caused trouble for the regime. Sulfosin was used to punish these dissidents and those mentally ill people who violated the discipline of psychiatric hospitals.<sup>65</sup> Mentally healthy people spent years secluded in psychiatric institutions receiving high doses of psychotropic drugs and sulfosin injections. Shock treatments, such as electroconvulsive therapy, insulin coma, and atropine were rarely used due to their technical complexity and to the fact that sulfosin and antipsychotic drugs were easier to use to maintain order at the centre.<sup>2,66</sup>

The “Sulfozin Cross” was used at psychiatric hospitals to punish for the most severe offences, such as theft, escape attempts, or assault of other inmates. It consisted of four injections administered at the same time below both scapulae and buttocks, with the patient tied to the bed. Another terrifying form of punishment was the combination of sulfosin with high doses of haloperidol, causing intense pain, high fever, and acute dyskinesias. Some centres had rooms with eight to 10 beds exclusively dedicated to patients receiving sulfosin (Figure 3). After a course of Sulfozin, inmates’ behaviour radically changed. Drug addicts described heroin abstinence as being like “the cry of a child on the grass” in comparison to *sulfa*, a name that came from the Russian pronunciation of Sulfozin (Сульфозин, “sulfagin”).<sup>27,61</sup> This has also led to the drug being mistaken in the English literature with Sulfazin, the commercial name of sulfasalazine, a drug used for inflammatory bowel disease.<sup>67</sup>

This practice was promoted based on the subjectivity of psychiatric diagnosis and the lack of objective tests. Many dissidents were accused of presenting sluggish schizophrenia, a concept developed by the Moscow School of Psychiatry, directed by Andrei Snezhnevsky, which provided a very useful framework to justify this



**Figure 3.** Sulphur day. Procedure for administrating sulfosin at a psychiatric hospital in the Soviet Union (cartoon by Jeannie Morton) (Source: <http://nonkill.info/phisicant/algogens.shtml>).

treatment. It was considered an independent diagnostic category and not a prodromal phase of schizophrenia. Symptoms included personality alterations with pessimism, poor social adaptation, or conflict with authority. Individuals with the condition were well adapted to social life but overestimated injustice and conceived grandiose ideas to reform society. They had an exaggerated idea of their own righteousness and believed that their rights had been trampled on. When they were examined by independent psychiatrists, no mental illness was detected.<sup>66</sup>

Many psychiatrists became researchers and jailers. Dissidents, accused of anti-Soviet agitation and propaganda, slander against the government, or hooliganism, were sent to the Moscow Serbsky Institute for mental examination. There, they were studied by specialists who could place them under medical custody if they considered the dissidents to present a mental illness, admitting them to high-security psychiatric hospitals, colloquially known as *psikhushkas* or psychoprisons, without the intervention of lawyers or courts. If they renounced their beliefs, they were considered to be cured. Thousands of Soviet citizens suffered psychiatric abuse and at least several hundred received Sulfozin and antipsychotic drugs at high doses.<sup>66</sup>

During Gorbachov's government, this repression was attenuated and a delegation of American experts visited the country in 1989. Its members could access psychiatric hospitals, consult clinical histories, and interview admitted patients, observing the repression suffered by individuals who had no mental illness.<sup>67</sup> With the collapse of the Soviet Union, systematic repressive psychiatry officially disappeared, though it remained active on some occasions.<sup>66</sup>

#### Sulfozin in Post-Soviet Russia

Sulfozin is not currently forbidden in Russia and other former Soviet republics. Order no. 470 of the USSR Ministry of Health of 15 August 1989, on the approval of the use of sulfosin and other shock therapies, limited the use of sulfosin, insulin coma, electroconvulsive therapy, and other similar treatments if there was no written consent from the patient or a legal representative. Furthermore, these treatments could only be indicated by a medical commission. This order remains in force today.<sup>27</sup>

Even in the 21st century, Bekker and Bykov reported two cases of schizophrenic patients who showed resistance to psychoactive drugs and other methods, in whom

remission was only achieved with Sulfozin injections. They considered that pyretotherapy, and particularly sulfozin, were cancelled too soon, as they may be useful in some cases, an opinion shared by some authors from Western countries.<sup>2,4,8</sup>

Since 2014, psychiatric repression has again increased in Russia, particularly affecting individuals who have positioned themselves against the annexation of Crimea. Some of the inmates of psychiatric hospitals may have witnessed how high doses of antipsychotic drugs continue to be used in prolonged treatments. Some human rights activists or anti-corruption protesters in Russia and other former Soviet republics are committed with a diagnosis of emotionally unstable personality disorder, the replacement for the former diagnosis of sluggish schizophrenia. Complaints have been made by inmates of colonies and prison hospitals in Omsk, Krasnoyarsk, Saratov, Vladimir, and others; they denounced beatings, electrical currents, burning, and other types of torture, as well as poisoning, economic extortion, and multiple injections of high doses of Aminazin (chlorpromazine), “Madam Depo” (Moditen Depot, fluphenazine), and Zalasta (olanzapine). However, there are no current reports on the use of sulfozin.<sup>2,68-70</sup>

#### Pyretotherapy in Western countries in the 21st century

In recent years, few cases of remission of a mental illness have been reported after febrile syndrome. In 2007, Sani et al.<sup>71</sup> published the case of a patient with a schizoaffective disorder of acute onset who after 12 days developed fever secondary to urinary tract infection; psychoactive drugs were suspended. When fever remitted, the psychotic symptoms also disappeared.<sup>71</sup> In 2016, Zuschlag et al.<sup>4</sup> reported the case of a woman with a schizoaffective disorder showing resistance to psychoactive drugs and electroconvulsive therapy, who started to improve after a bacteraemia with fever of 40°C. In reality, we should bear in mind that fever more often exacerbates or triggers psychotic breaks than improves them; therefore, the effect of fever on mental illness is ambiguous.<sup>71</sup>

Some authors have suggested that pyretotherapy should be reintroduced in some cases, and malaria inoculation has been trialled as a treatment for AIDS and Lyme disease. American patients with Lyme disease travel to Mexico to undergo malariotherapy. In 2014, researchers observed that African patients with coinfection of malaria parasites and Ebolavirus presented longer survival times.<sup>8</sup>

## Conclusions

Sulfozin has had an eventful journey over its 100 years of existence. Like other pyretotherapy agents, it had its golden age in the 1920s and 1930s. It was introduced as an alternative to malariotherapy for the treatment of neurosyphilis and other mental illnesses, due to the problems associated with malaria inoculation. Sulfozin was one of the safest and most reliable treatments for inducing fever, although injections caused intense local pain, which was alleviated with an anaesthetic.

The outcomes of treatment with sulfozin were moderate in general paralysis of the insane, a disease inevitably leading to death within a few years. Results were more modest and frequently contradictory in schizophrenia and other functional illnesses, which should be considered in the context of the time, when more effective options were not available. Several years later, the introduction of shock therapies in psychiatry and the use of penicillin for neurosyphilis replaced pyretotherapy treatments.

However, sulfozin continued to be used in the USSR, even after the appearance of modern psychoactive drugs in the mid-1950s. Although sulfozin was officially intended for therapeutic purposes, during the last 30 years of the Soviet Union, psychiatric hospitals used it as a disciplinary measure and to punish dissidents in the context of punitive psychiatry. It has since fallen into disuse, but it is still occasionally used today in Russia and other former Soviet republics.

## Conflicts of interest

The author has no conflicts of interest to declare. This is an original article. This study has not been presented at the SEN's Annual Meeting or at any other meeting or congress, nor has it been submitted to other journals. The author has received no public or private funding for this study.

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