

# Disulfiram - therapy of chonical infections

Experiences since November 2019

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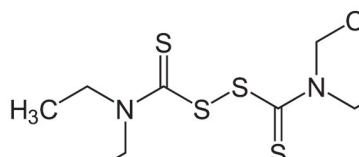


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## What ist Disulfiram?



**Disulfiram**, also **Tetraethylthiuramdisulfid** (TETD), (trade name *Antabus*®)



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## How does Disulfiram work?

### Historical:

- in the 19th century application in the vulcanization of rubber in rubber production
- 1937 Discovery of alcohol intolerance among factory workers



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## How does Disulfiram work?

- Rapid conversion of disulfiram to diethylthiocarbamate
  - Binding of metal ions with high affinity
  - Selective and irreversible inhibition of aldehyde dehydrogenase selectively
    - Degradation of alcohol only possible to acetaldehyde
- Inhibition of the enzyme dopamine- $\beta$ -hydroxylase
  - Increase of dopamine, decrease of norepinephrine in peripheral and central tissues

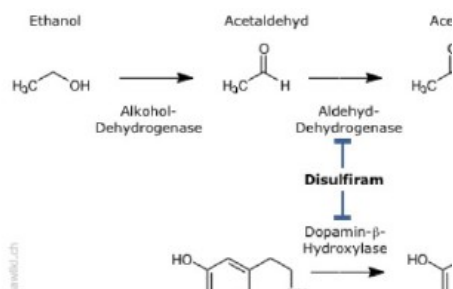


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## How does Disulfiram work?



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## Disulfiram and chronic Lyme disease

- first therapy of Lyme disease in 2017 by Dr. Liegner in 3 patients
- effectiveness against infection with Borrelia and Babesia
- insufficient efficacy against Bartonella

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## Disulfiram and chronic Lyme disease

### Patient group

- Treatment of approximately 70 patients treated with Disulfiram since November 2019.
- Patients with persistent symptoms or only partial success after years of therapy
- Many patients HLA-DR positive as genetic predisposition for antibiotic-resistant Lyme disease



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## Disulfiram and chronic Lyme disease

### Cave:

- Off-Label use!
  - therefore detailed patient information and documentation of the consent




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**Ermittlung zur Verwendung von Doxifram bei anhaltender Lyme-Borreliose Krankheit**

Doxifram ist ein Medikament, das hauptsächlich zur Reduzierung von Rückfällen bei Patienten mit Alkoholabhängigkeit eingesetzt wird. Es blockiert den Dopamin-Rezeptor im Gehirn, was Patienten schwer krank, wenn sie Alkohol trinken und während der Behandlung. Ursprünglich wurde es jedoch als Medikation für die Behandlung von sexuell übertragbaren Infektionen eingesetzt. In dieser Hinsicht ist es ein erneutes Interesse an der Wiederverwendung von Doxifram wurde als Behandlung von Staphylokokkeninfektion, Mycobacterium-Arten untersucht. Die Forschung zeigt, dass dieses Medikament bei der Behandlung resistenter Babesiose vielversprechend ist. Eine Fallbeschreibung von Dr. Bähle ist veröffentlicht. Es ist noch unklar, wie Doxifram antidiuretisch wirkt. Die Verwendung von Doxifram gegen Borreliose ist nicht kein Unternehmen hat die FDA oder eine andere Zulassungsbehörde (Zweck befragt).

**Wer sollte Doxifram nicht benutzen?**


- Patienten, die aktiv jede Form von Alkohol verwenden. Dazu gehören: Wein, Bier, Schnaps, Cocktails, etc. LESEN SIE IMMER DIE ANWENDUNGSANLEITUNGEN UND HANDBUCHLEITUNG! Der Alkoholkonsum sollte für mindestens 14 Tage während der Therapie und für mindestens 14 Tage nach der Therapie von Doxifram vermieden werden. Je länger ein Patient Doxifram einnimmt, desto stärker ist die Reaktion auf Alkohol.
- Patienten, die erhöhte Leberwerte zeigen oder die eine bestehende Lebererkrankung haben, einschließlich Leberzirrhose oder Leberversagen, einschließlich Todesfällen mit Doxifram.
- Schwangere Frauen. Obwohl es keine Berichte über Geburtschwierigkeiten bei Frauen oder Kindern nicht ausreichend untersucht.

**Wer kann es mit Vorsicht benutzen?**

- Patienten mit einer persönlichen oder Familienanamnese

1 Long TE. Repeating them and doxifram as antibacterial agents for chronic infections. Antimicrob Agents Chemother 2017; 61:e02088-17.  
 2 Lee SA et al. Population Pharmacokinetics and Pharmacodynamics of Doxifram in a Phase Ib Trial. Clin Pharmacol Ther 2019; 105:662-72.  
 3 Das S et al. Repeating doxifram to target infections caused by non-16S rRNA. Antimicrob Agents Chemother 2019; 13:1033.  
 4 Potluri VR et al. Identification of new drug candidates against Borrelia burgdorferi. Drug Discov Ther 2019; 13:1207-1232.  
 5 Legner KB. Doxifram (Tetrahydrofuran doxifram) in the treatment of Lyme disease: a case series. Antibiot (Basel). 2019; 8:872.

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**Nebenwirkungen:**  
 Eine vollständige Liste der Nebenwirkungen finden Sie die Besorgnis erregenden sind.

- **Leberversagen.** Dies ist ein seltenes Ereignis, das oder sogar zum Tod führen. Dies würde vorwiegend bei Patienten mit Lebererkrankung beobachtet werden. Wenn Sie Lebererkrankung haben, sollten Sie mit Ihrem Arzt besprechen, ob es neu gestartet werden soll. Da es ein stabiles Niveaus in Ihrem Blutkreislauf erreicht hat, ist alle 5-7 Tage.
- **Starke Juckreiz-Herzreizer-Reaktionen.** Die Tabletten können bei sehr niedrigen Dosen auftreten. Wenn Sie diese Tabletten nehmen, sollten Sie mit Ihrem Arzt besprechen, ob es neu gestartet werden soll. Da es ein stabiles Niveaus in Ihrem Blutkreislauf erreicht hat, ist alle 5-7 Tage.
- **Neuropathische Beschwerden**
- **Selbststörungen**
- **Schweißiger Körpergeruch**
- **Mehrere andere Nebenwirkungen wie Schläfrigkeit**

Alle Patienten müssen einer sorgfältigen Überwachung insbesondere in den ersten zwei Monaten nach dem Beginn der Behandlung und dann werden.


Die optimale Dosis und Dauer der Behandlung sind nicht bekannt. Die optimale Dosis ist 125 mg Tabletten zweimal täglich nach dem individuellen Behandlungsplan mit täglich 125 mg erreicht ist.

Ich habe die obige Broschüre über die Vorteile und Risiken der Alternativen dazu gelesen, einschließlich der Risiken bei unzureichender Behandlung gegeben. Meine Fragen sind beantwortet. Alle freien Stellen in diesem Dokument sind ausgefüllt.

Unterschrift \_\_\_\_\_ Datum \_\_\_\_\_  
 Name drucken \_\_\_\_\_ Geburtsdatum \_\_\_\_\_  
 Arzt \_\_\_\_\_ Datum \_\_\_\_\_

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**Consent for Use of Doxifram for Persistent Lyme Disease/TBD**

Doxifram is a medication primarily used to reduce relapse in patients with alcohol dependence. It blocks the dopamine receptor in the brain, which makes patients extremely ill if they drink alcohol while on the drug. However, it was initially used as a medication for the treatment of chronic infections. In this era of antibiotic resistance, there is renewed interest in repurposing drugs as anti-infectives, and Doxifram research over the past three years has shown promise of this drug in the treatment of Lyme disease and Babesiosis. One case series of three patients has now been published showing an antibiotic effect.

**Use against Lyme disease is off-label (i.e. no company has request approval for using it for this purpose).**

**Who cannot use it:**


- Patients who are actively using any form of alcohol. This includes all beverages, mouthwash, cooking wine, etc. ALWAYS READ LABELS OF SUPPLEMENTS AND TOPICAL PRODUCTS SUCH AS HAND SANITIZER. Consumption should be avoided for at least 12 hours before taking this drug for at least 14 days after stopping Doxifram. The longer a patient has higher the Doxifram dose, the stronger the reaction to alcohol will be.
- Patients who have elevated liver function tests or compromised liver function. Doxifram should be avoided in these patients.
- Patients, who elevated liver values show or who have existing liver disease, including liver failure, including liver failure, including liver failure, including liver failure.
- Pregnant women. Even though there have been no reports of birth defects in pregnant women or children.

**Who can use it with caution:**

- Patients with a personal or family history of psychosis.

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 2 Lee SA et al. Population Pharmacokinetics and Pharmacodynamics of Doxifram in a Phase Ib Trial. Clin Pharmacol Ther 2019; 105:662-72.  
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 4 Potluri VR et al. Identification of new drug candidates against Borrelia burgdorferi. Drug Discov Ther 2019; 13:1207-1232.  
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**Side effects:**  
 A full list of side effects can be found in the package insert from your pharmacy. The most concerning are:

- **Liver failure.** This is a rare occurrence but can result in need for liver transplantation or even death. This is most likely to happen in the first two months of treatment but can occur later, even after the drug is stopped. A summary of risk and intermittent use approval is available at <https://www.alviasana.com/medication>.
- **Psychosis.** This is a rare side effect thought to be due to a metabolic blocking of dopamine to norepinephrine. This is thought to be dose-dependent, the higher the dose the risk is.
- **Strong Jarrisch-Herxheimer reactions** which may last for days and even week medication is stopped. These will vary from patient to patient and may occur at 1-2 weeks after the drug is stopped. More information on this risk is available at <https://www.alviasana.com/medication>.
- **Neuropathic symptoms**
- **Visual disturbances**
- **Sweaty body odor**
- **Multiple other side effects** such as sleepiness, increased appetite, headache.

All patients must agree to careful monitoring of liver function, especially for the first two months of treatment and every 4 weeks thereafter.

**How to take Doxifram?**  
 The optimal dose and length of treatment are not known. Three to six months of treatment is recommended. The drug MUST be started at a low dose which is increased gradually. The drug MUST be started at a low dose which is increased gradually. The drug MUST be started at a low dose which is increased gradually. The drug MUST be started at a low dose which is increased gradually. The drug MUST be started at a low dose which is increased gradually.

I have read the above handout on the benefits and risks of the use of doxifram, I understand the risks and benefits of foregoing treatment with it. My questions have been answered in terms I understand. All blanks on this document have been filled in as of the time of my signature.

Signature \_\_\_\_\_ Date \_\_\_\_\_  
 Print Name \_\_\_\_\_ Date of Birth \_\_\_\_\_  
 Witness \_\_\_\_\_ Date \_\_\_\_\_

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## Disulfiram and chronic Lyme disease

**Cave:**

- Disulfiram not available in Germany, but prescription possible
  - Order via international pharmacy necessary
  - different dosages in different countries



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## Disulfiram and chronic Lyme disease

**Requirements for the therapy**

- Absolutely no alcohol consumption, in some cases already side effects due to the application of alcoholic solutions on the skin or inhalation of alcoholic vapors
- normal liver values
- Treatment of Candida problems before starting therapy because of alcohol production by fungi
  - strictly yeast- and sugar-free diet
  - possibly therapy with antimycotics necessary



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## Disulfiram and chronic Lyme disease

### Contraindications

- Alcohol abuse
- pathological liver values, known liver damage
- anamnestic or known in the family Psychosis
- contraindicated in pregnant women and children under 16 years of age



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## Disulfiram and chronic Lyme disease

### Therapy – Approaching the right dose

- when starting a complete stop of the previous antimicrobial therapy
  - Starting dosage 125mg, or 50mg or 62.5 mg
  - Gradual dosage: Initially 125mg or 50mg pr 62,5mg every 3rd day,
  - from the 3rd week every 2nd day
  - from the 5th week daily
- dose increase according to the patient's clinic:  
if there are indications of a pronounced Herxheimer's reaction →  
withdrawal of the dosage or pause with Disulfiram
- overall cautious dose increase necessary
- dosage in such a way that Herxheimer's reaction is just avoided



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## Disulfiram and chronic Lyme disease

### Therapy - Dosage

- **Dosage according to body weight** (Liegner recommendation):
  - 250mg for patients with 45-60 kg
  - 375mg for patients with 60-80 kg
  - 500mg for patients with more than 80kg
- **No blanket target dose** based on body weight:
  - Patients who are sufficiently treated with 75mg but also patients who need 500mg
  - dose of 250mg an increase of 50mg is recommended, as toxic side effects occur more often



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## Disulfiram and chronic Lyme disease

### Accompanying therapy

- Symptom-related therapy with food supplements
  - to reduce the neurotoxicity zinc high-dose (40-50mg daily)
  - to improve detoxification Lemon water, glutathione, alkaline foot baths
  - to prevent the Herxheimer reaction Vitamin C, selenium, nicotinamide, NAD
  - to reduce inflammation of the brain Curcuma, Omega-3-FS, CBD



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## Disulfiram and chronic Lyme disease

### Accompanying therapy

- case-specific addition of antimicrobial herbs such as Artemisia annua
- Probiotic not necessary, but better tolerance, especially with regard to possible gastrointestinal side effects when using a probiotic



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## Disulfiram and chronic Lyme disease

### Side effects

- |  |                                |
|--|--------------------------------|
| - pronounced Herxheimer reactions              | - Tiredness                    |
| - Liver Failure                                | - Nausea                       |
| - Psychosis                                    | - Acne                         |
| - Neuropathies                                 | - metallic taste               |
| - Visual disorders                             | - Skin redness                 |
| - sulfur-like body odor                        | - reduced libido               |
| - Insomnia                                     | - Depression                   |
| - increased appetite but also loss of appetite | - Constipation and flatulence  |
| - Headache                                     | - hyperthyroid metabolic state |
|  | - Menstrual disorders          |



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## Disulfiram and chronic Lyme disease

### Toxic Effects:

- severe neuropathies
  - severe visual disturbances as an expression of an inflammation of the optic nerve
  - severe disturbances of balance as an expression of an inflammation of the vestibulochlear nerve
  - severe mental disorders
  - breathing problems
  - liver Failure
- **immediate stop of the therapy**, sometimes for weeks, symptoms so far always reversible, supplementation of the therapy with glutathione and alpha lipoic acid



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## Disulfiram and chronic Lyme disease

### ToDoes during therapy:

- regular monitoring of liver values and blood count, initially weekly, after 4 weeks 2-weekly
- regular appointments with the patient every 2-4 weeks



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## Disulfiram and chronic Lyme disease

### Results

After 4-6 months, first results in a total of 70 patients...

- partly significant improvement in 37 patients (53%)
  - in particular improvement of previously therapy-resistant symptoms such as chronic fatigue syndrome, brain-fog
  - significant improvement of CD57 values as an indicator for a recovery of the immune system, decrease of infectiological values in Elispot



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## Disulfiram and chronic Lyme disease

### Results

After 4-6 months, first results in a total of 70 patients...

- **Termination of therapy** in 13 patients (**19%**) due to severe side effects (partly severe psychosis, neuropathy, inflammation of the optic nerve with visual disturbances, walking disorders, breathing problems, pronounced elevation of liver function)
- **no effect** in 20 patients (**28%**)



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## Disulfiram and chronic Lyme disease

### Combined therapy with antibiotics

- one patient in combination with Doxycycline
- one patient in combination with rifampicin, azithromycin

### but...

- In vitro efficacy of disulfiram against *Borrelia Burgdorferi* but not against the stationary phase has been demonstrated.
- Combination e.g. of Cefuroxime + Clarithromycin more effective than the combination of Cefuroxime + Disulfiram



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## Disulfiram and chronic Lyme disease

### Conclusion

- partly therapy successes of patients, who had only limited success with antibiotics or herbs under previous regimens
- especially therapy option for patients who are HLA-DR positive and thus have a genetic predisposition for antibiotic-resistant Lyme Borreliosis
- no "standard dosage": therefore start with low dosages and approach the optimal dosage, from 250mg daily increase in 50mg steps
- ideally intake of Disulfiram in a capsule soluble in small intestine



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## Disulfiram and chronic Lyme disease

### Conclusion

- therapy must be accompanied by an experienced doctor
- regular monitoring of the liver values and blood count during the therapy
- enough time for the therapy necessary
  - sometimes first effect visible only after four months
  - therapy duration of at least six months recommended
  - termination of therapy when symptoms are free and laboratory values normalize



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## Disulfiram and chronic Lyme disease

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## Disulfiram and chronic Lyme disease

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## Sigrid Blehle, MD, MBA

- Study of human medicine in Giessen, license to practice medicine 1989
- Specialist for general medicine since 1995
- held various management positions and worked in consulting within and outside the health care system in Germany
- 2010 -2011 studies of health economics with degree in health economists (ebs) and M.B.A. Health Care Management
- Experience in the field of rheumatology and autoimmune diseases
- 2017-2020 BCA-Clinic, Augsburg, Germany, recently as partner in the private practice of Dr. C.Nicolaus/S.Blehle
- since 04/2020 own practice Alviasana, Augsburg, Germany - after closing of the BCA-Clinic take over the treatment of BCA patients
- member of the German Borreliosis Society and ILADS



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