Anti-TB drugs and Alcohol Interactions

Peculiarities of the safety profiles of anti-tuberculosis drugs in patients with alcohol-induced damage to organs and systems

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Key Issues

- Cardiotoxicity of anti-tuberculosis drugs in patients with alcohol-induced cardiovascular disorders. Approaches to monitoring and risk management.
- Neurotoxicity of anti-tuberculosis drugs in patients with alcohol-induced peripheral nervous system damage. Approaches to monitoring and risk management.
- Hepatotoxicity of anti-tuberculosis drugs in patients with alcohol-induced liver damage. Approaches to monitoring and risk management.

Mechanisms of Alcohol-Induced Cardiovascular Damage

Alcohol abuse

≥ 60 g / day

Individual modifying risk factors: behavioural, genetic, biological, type of abuse

Cardiomyocytes

Coronary arteries

Peripheral arteries

Mitochondrial dysfunction
Circulation abnormalities
Inflammatory response
Oxidative stress
Apoptosis
Direct damage to the cardiomyocytes
Affecting clotting factors
Changes in the mechanisms of ischemia-reperfusion regulation
Insulin resistance
Endothelial dysfunction
Reduced contractility (reduced activity of myofibrillar ATPase, sensitivity of myofibrils to Ca, intracellular exchange of Ca ions)

Hypertension

Coronary arteries disease (MI)

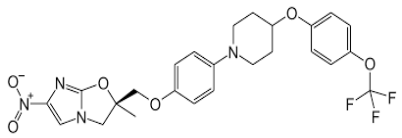
Peripheral artery disease

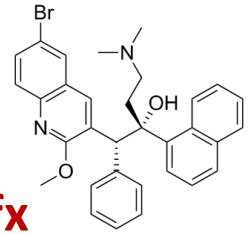
Cardiomyopathy
(LV expansion, change in the wall thickness and increase in LV mass index, decrease in LV ejection fraction**)**

Cardiac arrhythmias

Marianu K.Piano Alcohol's Effect on the Cardiovascular system. Alcohol Res.2017

Mechanisms of Proarrhythmic and Cardiotoxic Effects of Anti-tuberculosis Drugs





Bdq, Dlm, Cfz, Mfx

QT-interval prolongation *(HERG-potassium channels)*

QT-interval prolongation, dysrhythmia / conduction abnormality

Localized/ generalized **changes in the myocardium**, hypertrophy, overload of the compartments of the heart, acute coronary insufficiency, acute heart failure, progression of HF, etc.

Account for the majority of serious treatment-related outcomes

Potentially life-threatening

Bdq

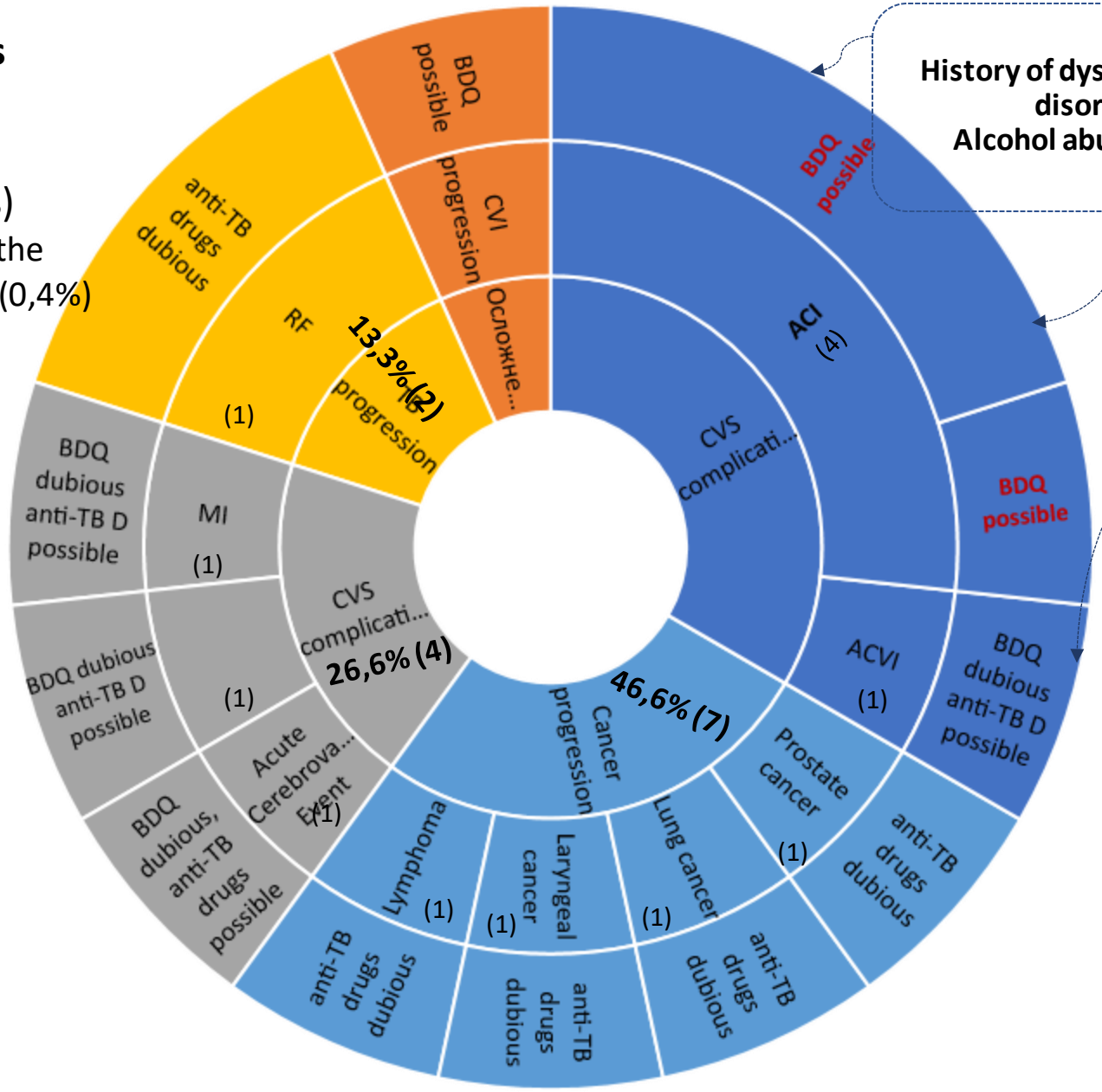
Direct cardiomyotoxic effect

Alcohol-induced cardiomyopathy, coronary artery disease, dysrhythmia

Risk factors
- History of ischemic /dysmetabolic disorders and dysrhythmia)
- age
- alcohol consumption
- electrolyte disorders
- drug interaction

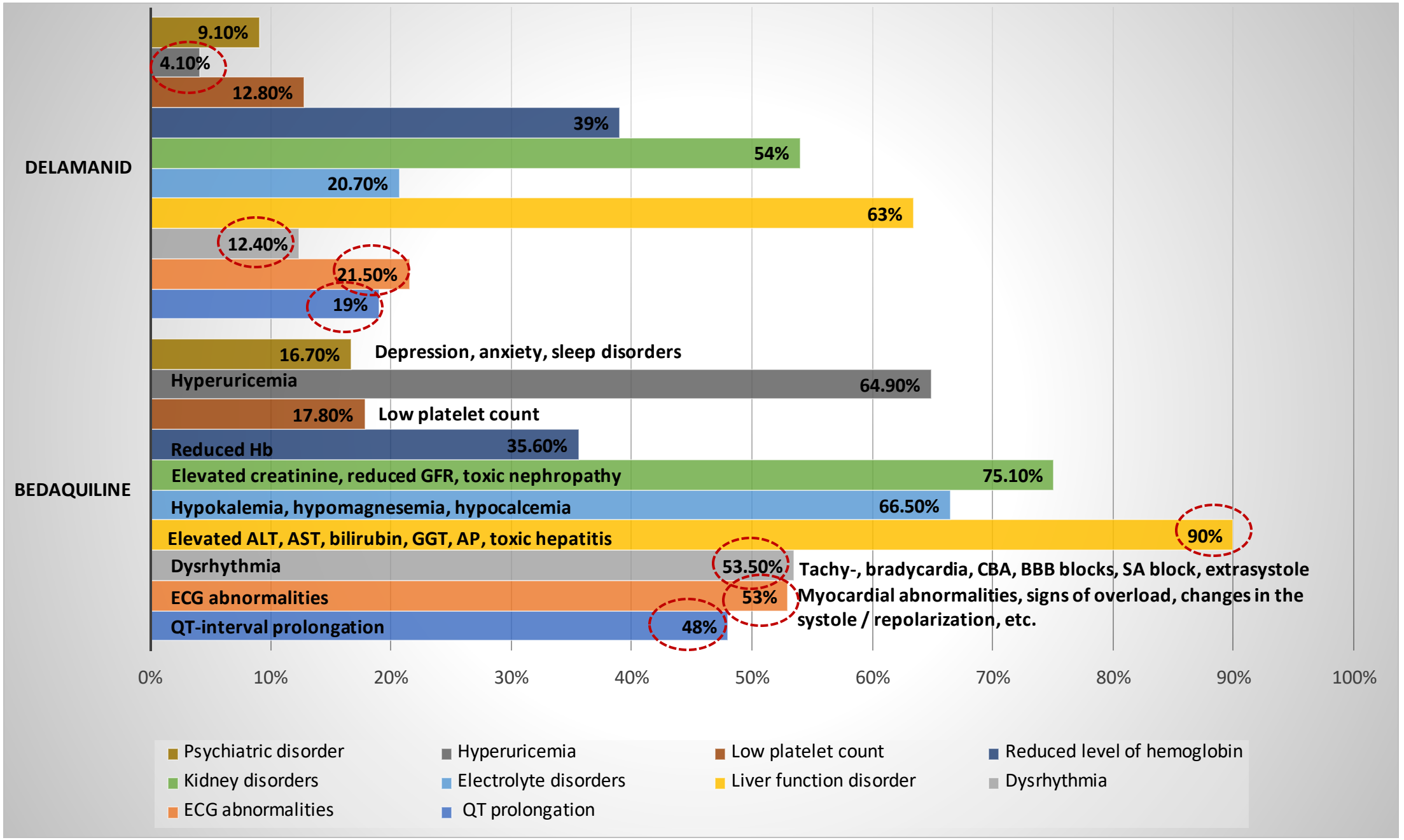
New Treatment Regimens' Safety Profile: Deaths

Bdq + anti-TB drugs
2.1 % (16)
deaths
(out of 763 patients)
Association of Bdq with the outcome not ruled out in 3 (0,4%) SAEs



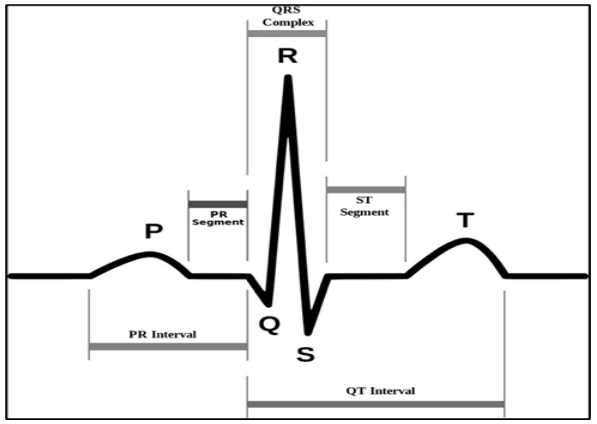
History of dysmetabolic/ ischemic heart disorders, heart failure
Alcohol abuse during treatment (2)

New Treatment Regimens' Safety Profile: Most Frequent AEs

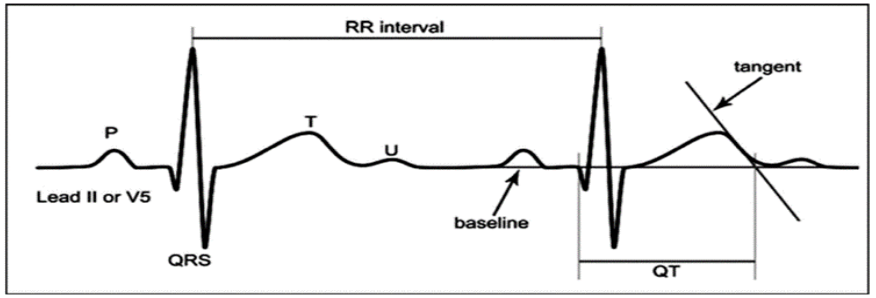


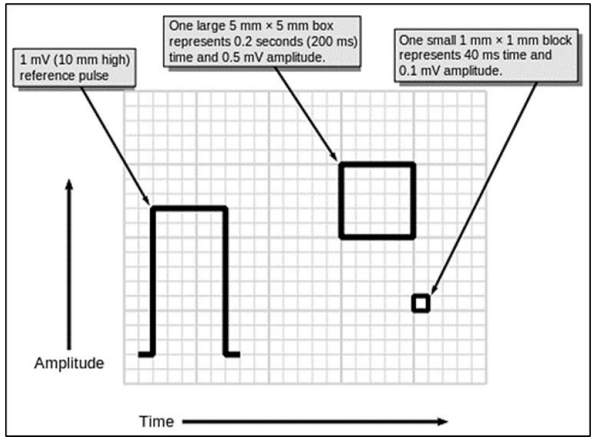
Routine Minimal Monitoring of Cardiotoxicity and Rhythm Disturbances

Monitoring and Evaluation	Recommended frequency
ECG	**Prior to the start of treatment with Bdq or Dlm, then at least 2, 4, 8, 12, and 24 weeks after the start of treatment. ECG monitoring should be performed monthly if other QT-interval prolonging medications (Mfx, Cfz) are taken.**
Serum potassium, magnesium, calcium	**Before the start of treatment and then monthly in patients on Bdq, Dlm.** It is repeated when ECG abnormalities are detected (prolongation of the QT interval). Every 1-3 weeks in patients with HIV infection, diabetes and patients at risk.
Albumin	**Prior to the start of treatment, then regularly in patients on Dlm** (risk of prolongation of the QTcF interval)



$$QT_{cF} = \frac{QT}{\sqrt[3]{RR}}$$

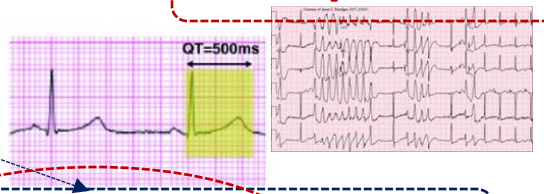




AE Management: QT-Interval Prolongation

Bdq, Dlm, FQs, Cfz

QTcF INTERVAL PROLONGATION



450 m (470 f) msec or 60 msec of the baseline > QTcF ≤ 500 msec

Confirmed by repeat measurement

Serum electrolytes (K^+, Ca^{2+}, Mg^{2+})

K^+, Ca^{2+}, Mg^{2+} withing normal range
Patient is stable

Continue the drug
Weekly (minimum) monitoring of QTcF

K^+, Ca^{2+}, Mg^{2+} outside the normal range

Discontinue Bdq (and injectable agents)
Restore electrolytes
Weekly (minimum) monitoring of QTcF

QTcF > 500 msec

Confirmed by repeat measurement

Discontinue Bdq, Dlm and other drugs that prolong QT-interval

Measure and maintain serum electrolytes within the normal range (K^+, Ca^{2+}, Mg^{2+})

Weekly (minimum) monitoring of QTcF

Kidney and liver function test

QT-Interval Prolongation: Risk Factors

Drugs that cause QT Interval Prolongation

Anti-infectious	Antiarrhythmic	Antipsychotic	Opioid analgesics	Antiemetic	Antidepressants	Proton pump inhibitor
Clarithromycin **Erythromycin** **Chloroquine** **Hydroxycloroquine** **Pentamidine** Azithromycin Roxithromycin Telithromycin **Moxifloxacin** Amantadine Gatifloxacin	**Amiodarone** **Disopyramide** **Dofetilide** **Ibutilide** **Procainamide** **Quinidine** **Sotalol**	**Chlorpromazine** **Haloperidol** **Risperidone** **Quetiapine** Sertindole Ziprasidone Lithium Clozapine Olanzapine **Thioridazine**	Methadone	Ondansetron Dolasetron Granisetron	Escitalopram **Venlafaxine** **Amitriptyline** **Desipramine** **Imipramine** **Sertraline**	Omeprazole Esomeprazole Pantoprazole

Risk factors for hypokalemia and hypomagnesemia

Loop and thiazide-type diuretic	Furosemide, hydrochlorothiazide, indapamide
Nephrotoxic drugs	Aminoglycosides, amphotericin B, cisplatin and others
Renal tubular transport disorder Alcoholism Diarrhea, vomiting	

Additional Mitigation Measures in Patients With Alcohol-Induced Cardiovascular Damage

Hypertension

Coronary arteries disease (MI)

Cardiomyopathy

Cardiac arrhythmias

Treatment start

- **Additional individual assessment of the benefit-risk ratio**, taking into account alternative options
- **Extended cardiac evaluation**
- **Consultation with a cardiologist** for evaluation **at the stage of enrollment, monitoring and detection of abnormalities**
- **Increasing the frequency of ECG and electrolyte monitoring** (up to several times a week), closer monitoring of the indicators of worsening of the cardiac pathology
- **Assessment and minimization of other risk factors** (alcohol consumption, revision of concomitant therapy, etc.)
- **Immediate measures upon detection of abnormal parameters**
- **Informing the patient about the high risk of cardiac disorders** (during treatment and for several months after its completion) and the **symptoms of deterioration** (tachycardia, palpitations, fainting, dizziness, weakness)

Treatment end

Mechanisms of Alcohol-Induced Damage to the Peripheral Nervous System

Alcohol abuse

≥ 60 g / day

Individual modifying risk factors: behavioural, genetic, biological, type of abuse

- Oxidative stress
- Free radical-induced damage to peripheral nerve fibers
- Spinal cord microglial activation
- Activation of mGlu5 receptors of the spinal cord
- Activation of the sympathicoadrenal hypothalamic-pituitary system
- Nutritional deficiency (impaired absorption and phosphorylation of thiamine, decreased thiamine depot in the liver)
- Axonal degeneration
- Decrease in the density of nerve fibers
- Segmental demyelination

Potentially disabling

Alcohol-induced neuropathy (spontaneous burning pain, hyperalgesia, numbness, allodynia, loss of vibration sense, muscle weakness)

Elevated risk and severity of neuropathy

Mitochondrial toxicity

Lzd
Cs, FQs

K.Chopra et al. Alcoholic neuropathy: possible Br J Clin Pharmacol.2012

Routine Monitoring of Patient's Safety

I. Brief screening for peripheral neuropathy (CPN) before and during treatment

В норме	Легкий ---------- Тяжелый									
00	01	02	03	04	05	06	07	08	09	10

The patient evaluates the severity of each symptom on a scale from 01 (mild) to 10 (extremely severe) for the right and left feet and legs

Симптомы	П	Л
a. Острая или тупая боль или жжение в стопах, ногах		
b. Покалывание в стопах, ногах		
c. Онемение (утрата чувствительности) в стопах, ногах		

Индекс субъективной тяжести сенсорной нейропатии	Степень тяжести
00	0
01 – 03	1
04 – 06	2
07 – 10	3

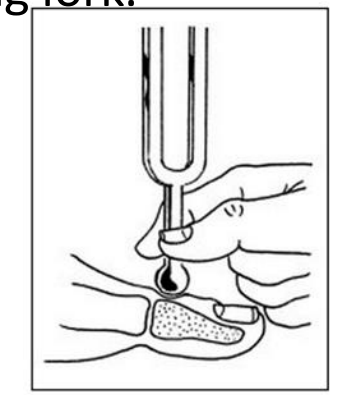
To determine the subjective index of severity of sensory neuropathy, the highest of the obtained symptoms scores is used

Patient’s Safety Monitoring Procedure

II. Testing vibration sense

Place together the ends of the 128 Hz tuning fork so that their sides barely touch.

Place a vibrating tuning fork on a bony prominence on the patient's arm or wrist to make sure that the patient recognizes the vibration or the "hum" of the tuning fork.



Immediately after that, carefully move the turning fork and press it tightly to the upper part of the distal interphalangeal joint of the big toe and start counting the seconds.

Ask the patient to indicate when the vibration stops.

Repeat for another toe.

Восприятие вибрации	Результат	Баллы
Ощущается > 10 с	В норме	0
Ощущается 6–10 с	Легкое снижение	1
Ощущается < 5 с	Умеренное снижение	2
Не ощущается	Сильное снижение	3

III. Assessment of deep tendon reflexes

Assessment and Management of Peripheral Neuropathy

Severity grade*	Grade 1: Mild	Grade 2: Moderately severe	Grade 3: Severe	Grade 4: Life-threatening
Paraesthesia (burning, tingling, etc.)	Mild discomfort: no treatment is required; index of subjective severity of sensory neuropathy according to the BSPN* on either side is 1-3.	Moderate discomfort; non-narcotic analgesia is required; and/or the index of subjective severity of sensory neuropathy according to the BSPN* on either side is 4-6.	Severe discomfort; or narcotic analgesia is required to alleviate the symptoms; and/or the index of subjective severity of sensory neuropathy according to the BSPN on either side is 7-10.	Disabling or refractory to narcotic analgesia
Action	**Discontinue Cs/Trd and Lzd. If symptoms are improved, consider reintroduction of these drugs. Consider restarting Lzd at a lower dose (300 mg per day or 600 mg three times a week).** If Cs/Trd are not mandatory in this regimen, consider discontinuation of these drugs.	**Discontinue Cs/Trd and Lzd. If the symptoms improve, and these drugs are required in this regimen, consider reintroduction of Cs/Trd**. **Do not restart Lzd.** Provide symptomatic treatment as indicated below.	The same as for grade 2.	The same as for grade 2.

Lzd, Cs/Trd, H, S, Km, Am, Cm, FQs, редко - Pto/Eto, E

*** Brief screening for peripheral neuropathy**

Additional Measures to Mitigate the Risk in Patients With Alcohol-Induced Nervous System Damage

Alcohol-induced neuropathy

Treatment start

- **Additional individual assessment of the benefit-risk ratio**, taking into account alternative options
- **Expanded neurological examination**
- **Consulting with a neurologist** for evaluation **at the stage of enrollment, monitoring and identification of deviations**
- **Higher frequency of monitoring**, paying attention to the signs of deterioration of the neurological status
- **Assessment and mitigation of other risk factors** (alcohol)
- **Taking immediate measures upon detection of abnormalities**
- **Informing the patient about the high risk of neurological disorders**
- **Preventive intake of B6 vitamin**

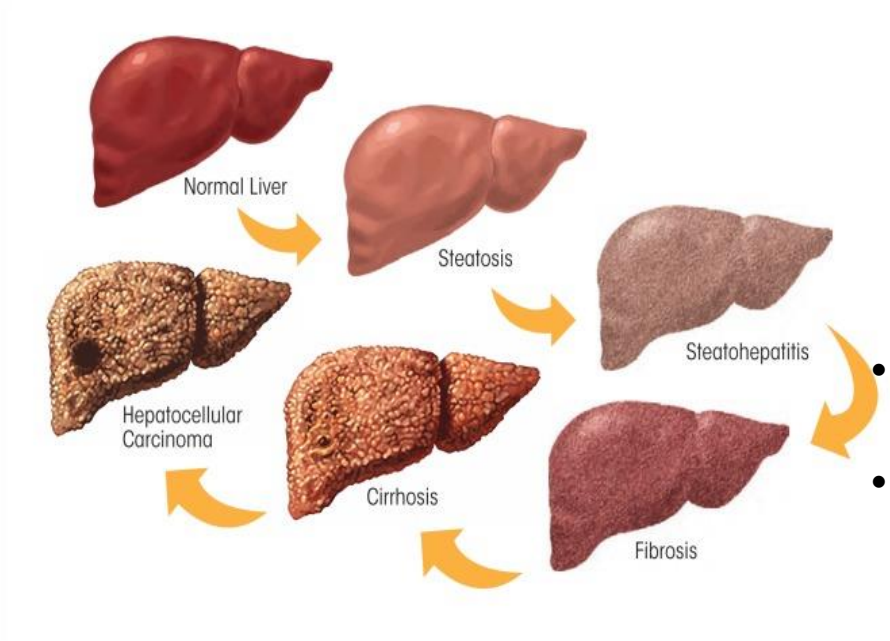
Treatment end

Mechanisms of Alcohol-Induced Liver Damage

Alcohol abuse

≥ 60 g / day

Individual modifying risk factors: behavioural, genetic, biological, type of abuse



- Oxidative stress
- Free radical-induced damage of hepatocytes
- Hepatocyte lipid deposition – steatosis
- Inflammatory liver damage-steatohepatitis (up to 35%)
- Fibrosis
- Cirrhosis (8-20%)

Hepatitis

Elevated risk and severity grade

Bdq, FQs

K.Chopra et al. Alcoholic neuropathy: possible Br J Clin Pharmacol.2012

Routine Minimal Monitoring of Hepatotoxicity and Pancreatotoxicity

Monitoring and evaluation	Recommended frequency
ALT, AST, bilirubin	**Before the start of treatment and then monthly in patients on Bdq**. In patients with viral hepatitis - every 1-2 weeks during the first month and then every 1-4 weeks. **γ-GGT** is a more sensitive marker of alcohol-induced liver damage. AST:ALT >2 (up to 80% of patients with alcohol-induced liver damage)
Lipase	**Prior to the start of treatment with Bdq.** In case of abdominal pain in patients on Lzd, Bdq, D4T, ddI, ddc

Additional measures to minimize the risk of alcohol-induced liver damage in patients

- **Informing the patient about the high risk of liver disorders**
- **Replenishment of nutritional deficiency (protein intake of 1.5 g / kg, 35-49 kcal/kg, trace elements (Se, Zn, CU, Mg)**
- **Assessment and mitigation of other risk factors (alcohol, concomitant therapy, etc.)**
- **Increasing the frequency of monitoring of hepatotoxicity biomarkers**

Management of AEs: Hepatotoxic Events

Z, H, R, Pto/Eto, Bdq, PAS

Elevated ALT, AST, bilirubin

ALT, AST elevation > 3 times the upper threshold

Repeat the measurement in 48 hours

Consider the possibility of discontinuing other hepatotoxic drugs, eliminating other factors (alcohol)

+ elevated bilirubin > 2 times the upper threshold

Persistence > 2 weeks

Discontinue Bdq
Monitor until the parameters improve
Consider reintroduction

ALT, AST elevation > 5 times the upper threshold

All hepatotoxic drugs are stopped

Lack of improvement within 3 days – discontinue all medications

Assessment and elimination of other factors resulting in deterioration of liver function – the most common: viral hepatitis (A, B and C) and alcohol consumption (stop consumption)

Control of parameters till they improve (1 time every 3 days)

Reintroduction of drugs (gradual) from less to more hepatotoxic with proper control every 3 days. Replacement if possible

Conclusion

- Patients with alcohol-induced cardiovascular system, peripheral nervous system and liver damage are at higher risk of experiencing serious adverse events when taking anti-tuberculosis drugs.
- In order to reduce the risk of life-threatening reactions in patients with alcohol-induced disorders, additional monitoring and risk management measures are required.
- There are country differences in the characteristics of patient cohorts by alcohol consumption and alcohol-induced disorders of organs and systems.
- Better understanding of safety profiles of new anti-tuberculosis drugs in patients with alcohol-induced disorders of organs and systems is necessary to identify the best strategy to mitigate the risks of adverse treatment outcomes.

Thank you for your attention!

Questions?