

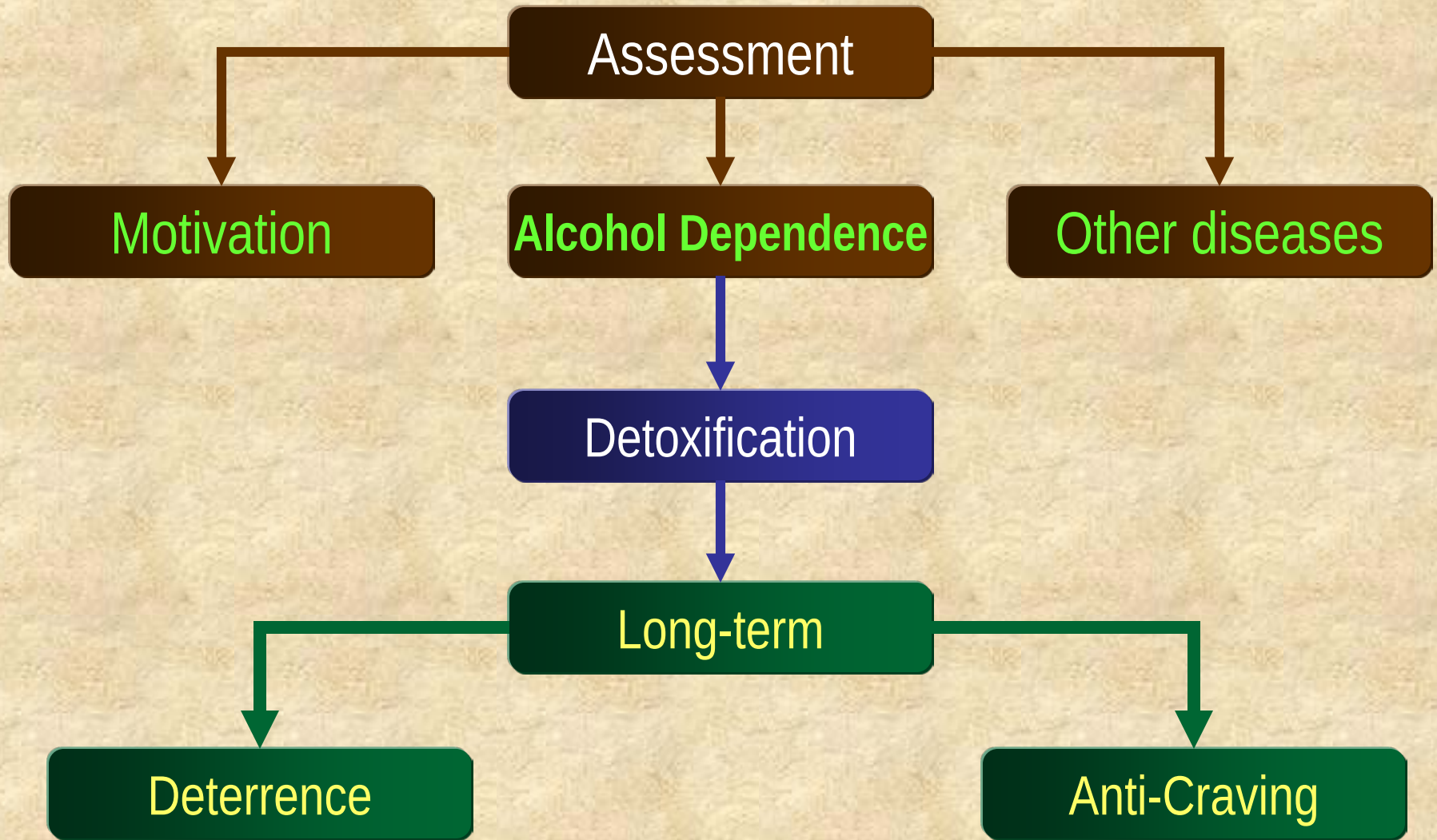
Long term pharmacotherapy for Alcohol Dependence: Anti Craving agents

Myth or Reality ?

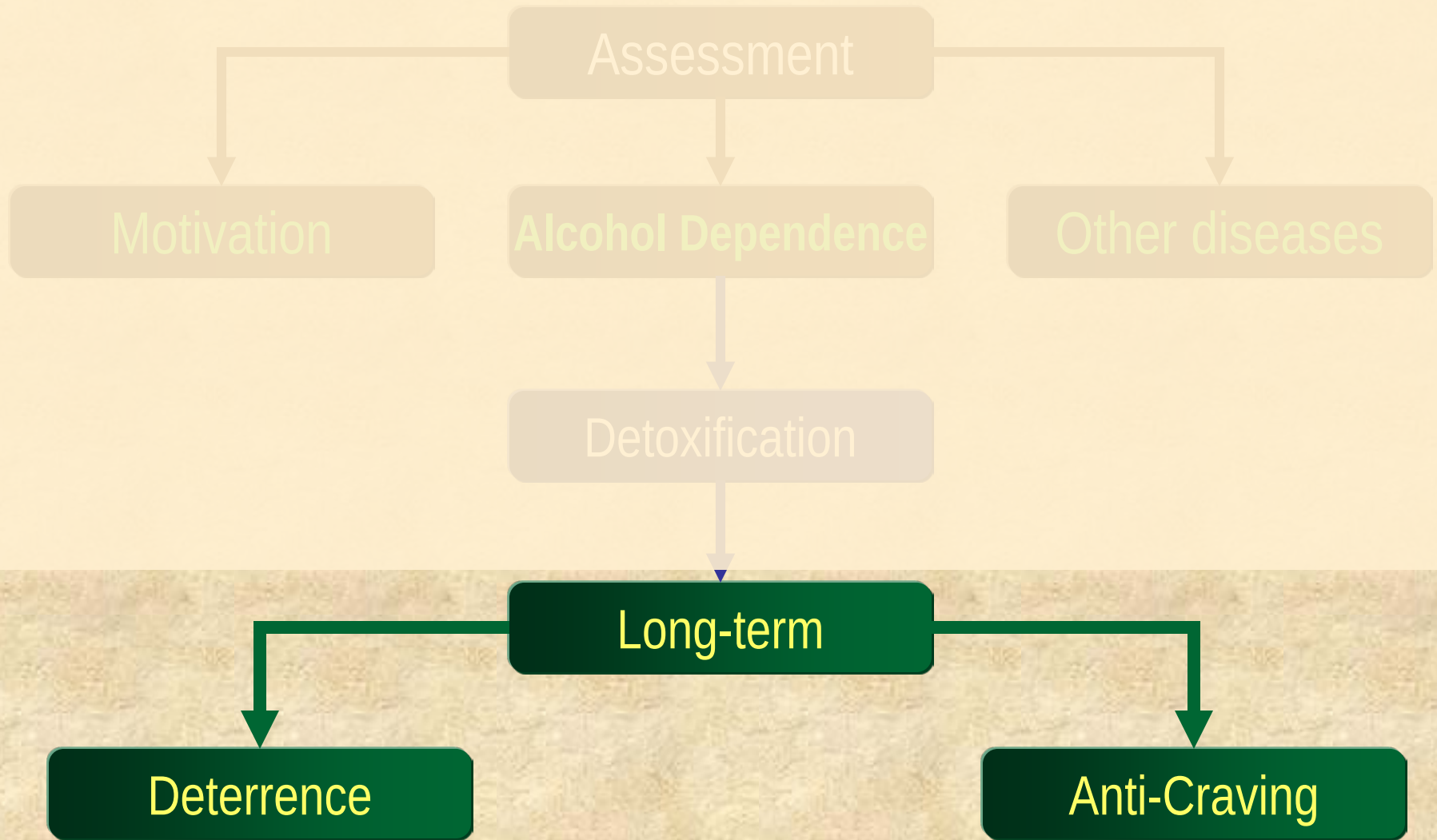
Complete Recovery means a medication-free state

☐ *True or False?*

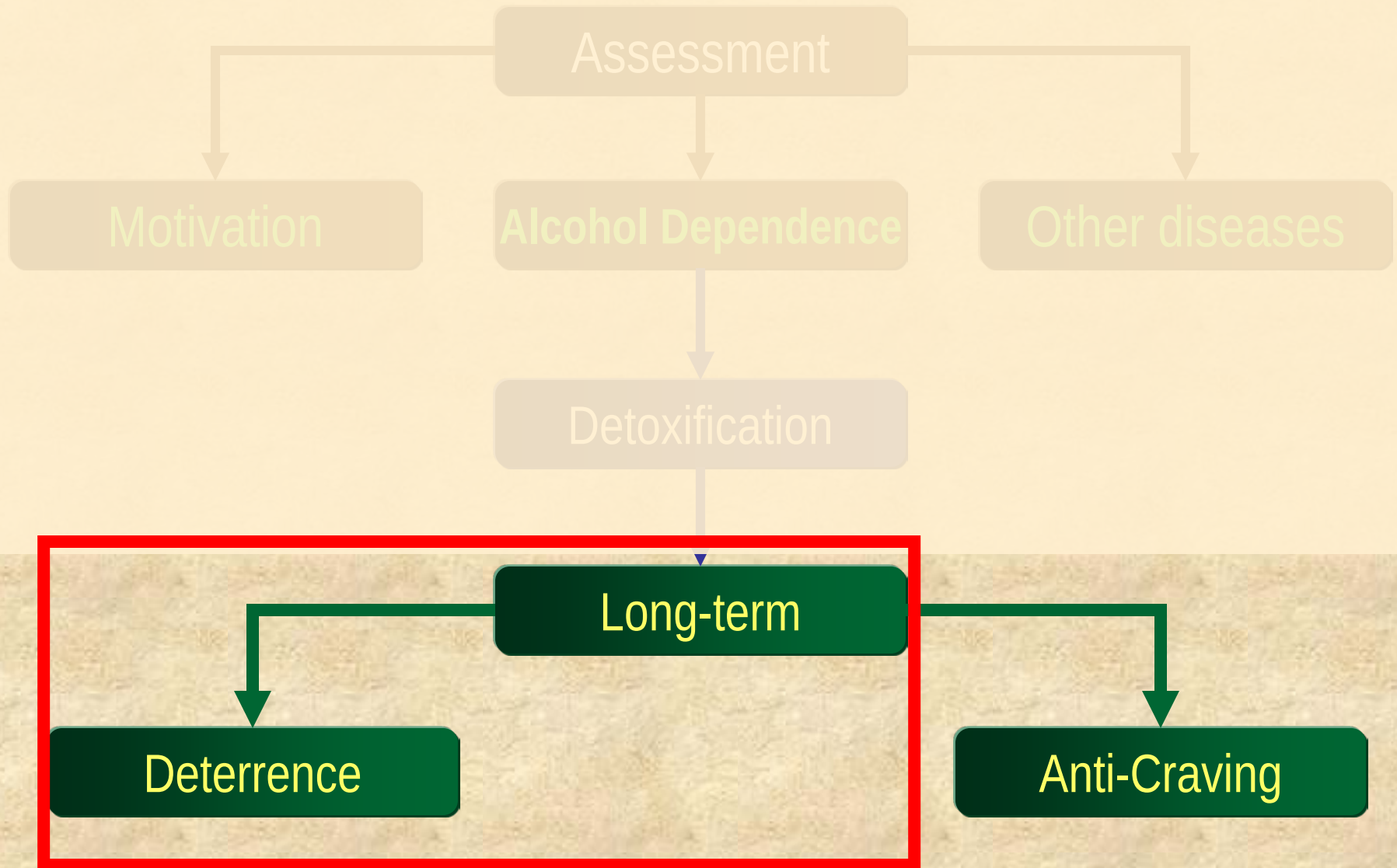
Treatment of Alcoholism



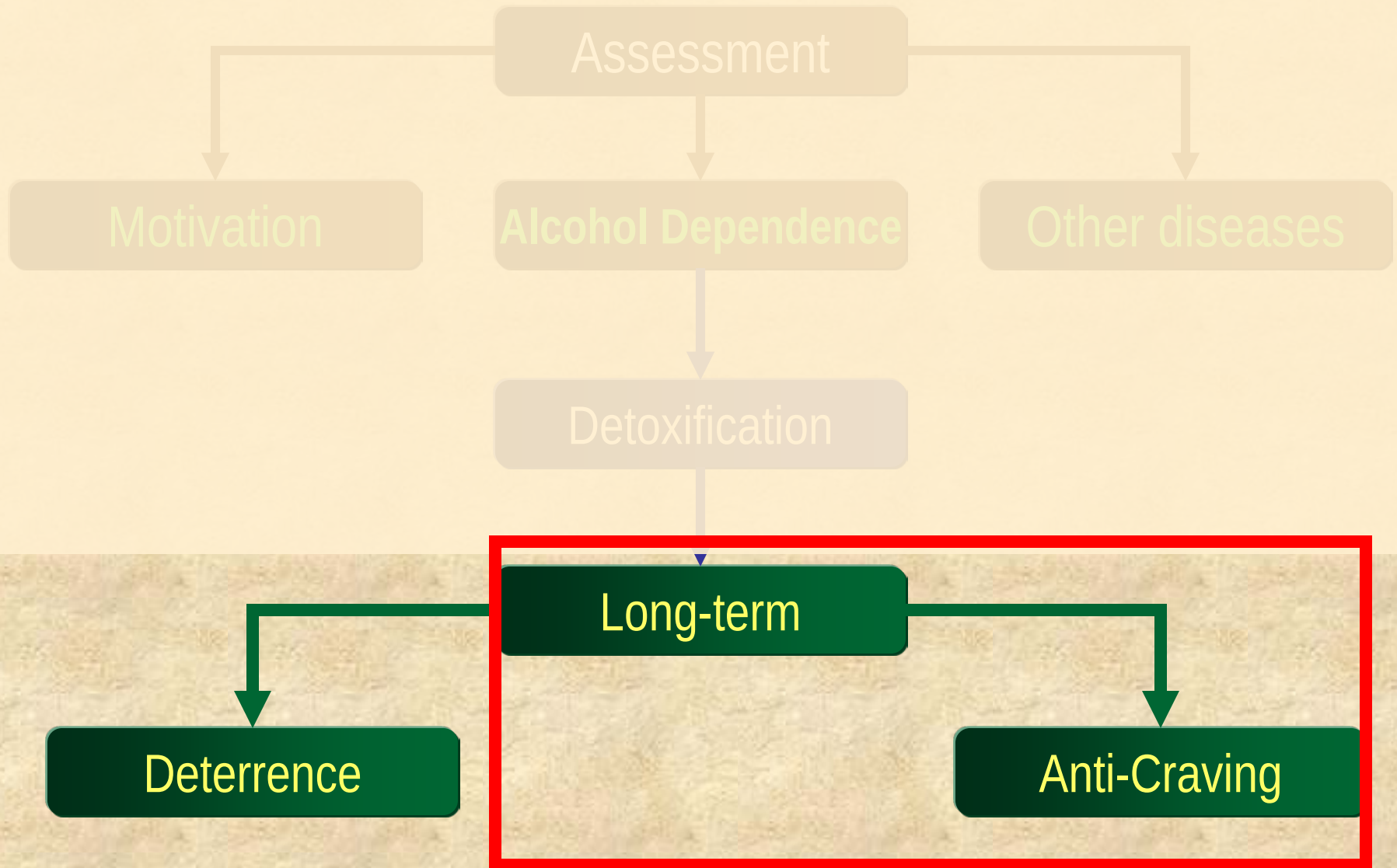
Treatment of Alcoholism



Treatment of Alcoholism

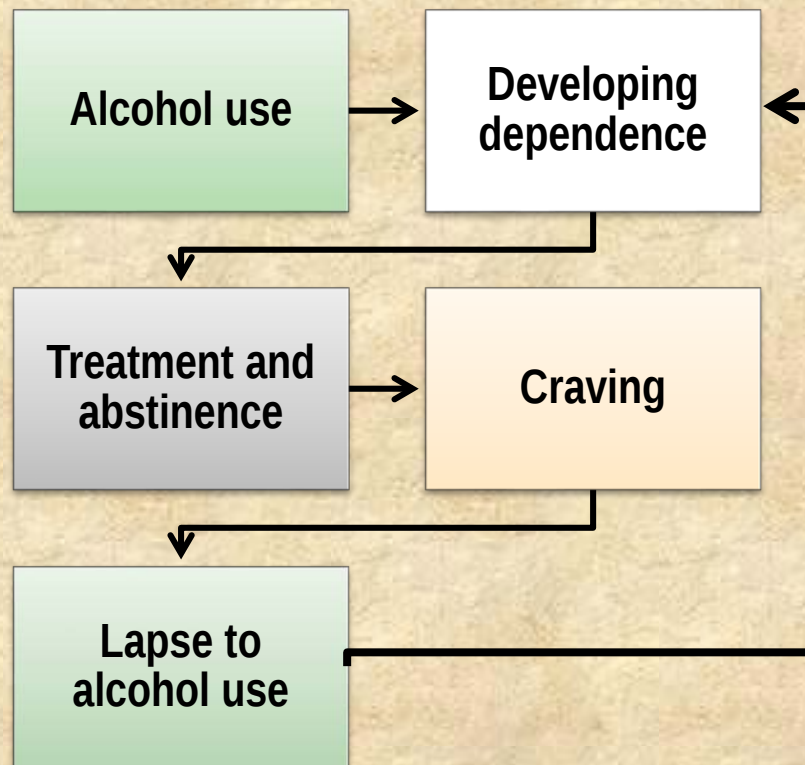


Treatment of Alcoholism

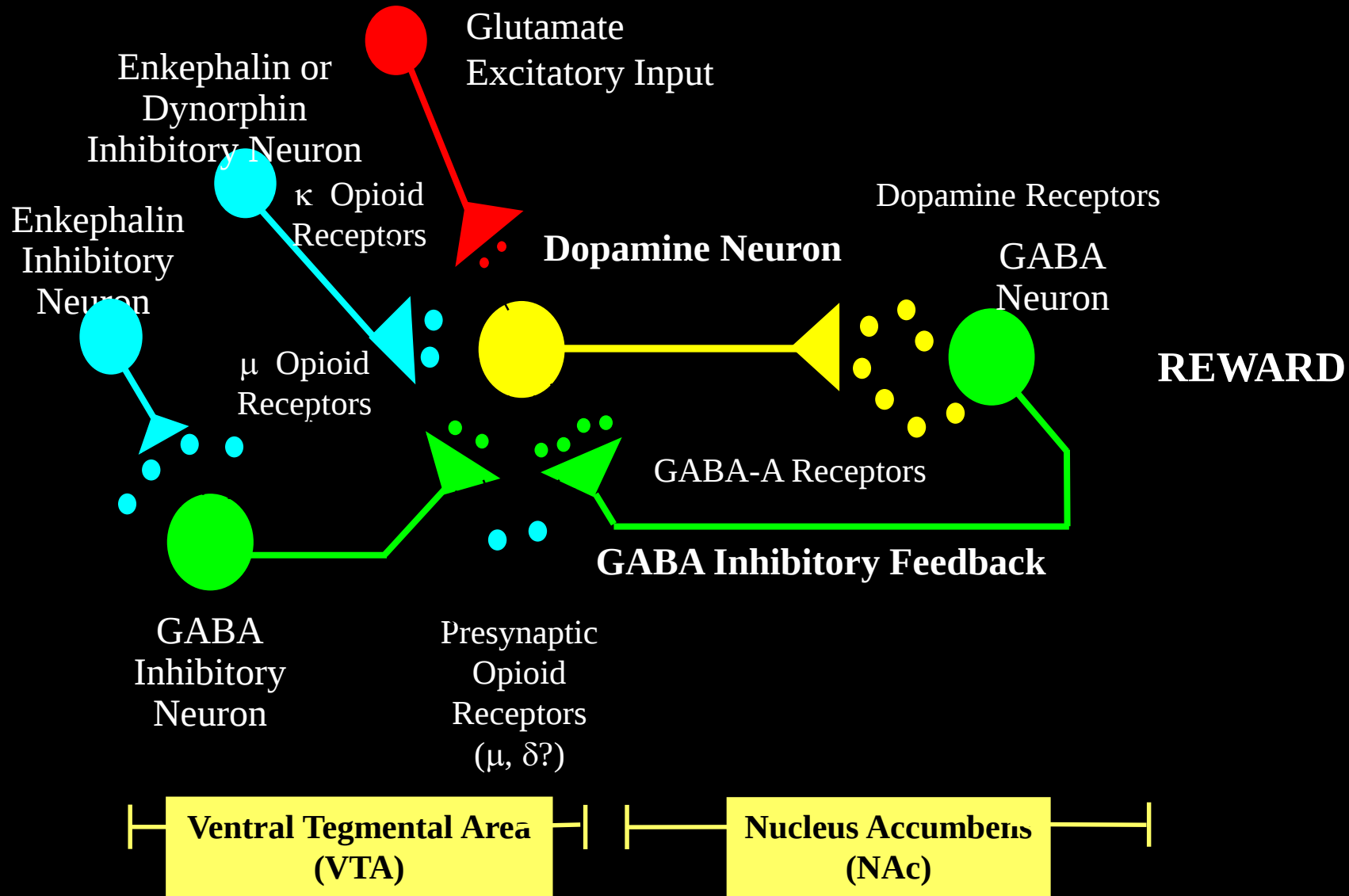


What is craving?

❑ Craving: Strong urge or desire



Reinforcement: Neurochemical systems



Neurotransmitters and Alcohol Dependence

- ☐ Opioids
- ☐ Glutamate
- ☐ GABA
- ☐ Serotonin

Neurotransmitters and Alcohol Dependence

☐ Opioids

Naltrexone

☐ Glutamate

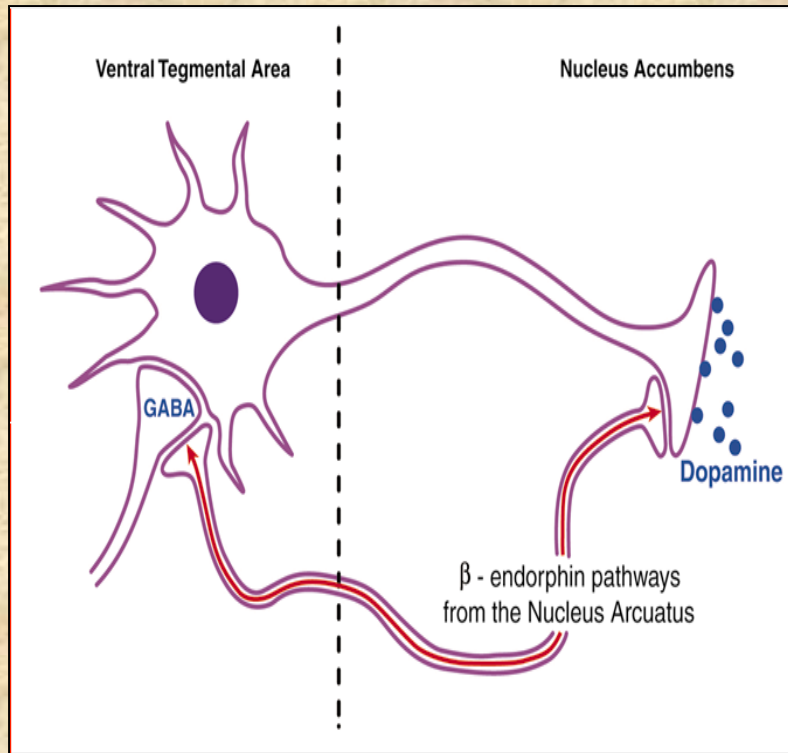
☐ GABA

☐ Serotonin

Naltrexone

- ❑ Opioid antagonist
- ❑ Oral 50 mg tablets
- ❑ Role in Alcohol Dependence:
 - ❑ Decreases alcohol craving, rate of relapse, and length of drinking episodes
 - ❑ Studies combined medication with psychosocial supports

Naltrexone: Basic science



Embellished from Gianoulakis 1998

Alcohol affects the production, release, and activity of opioid peptides



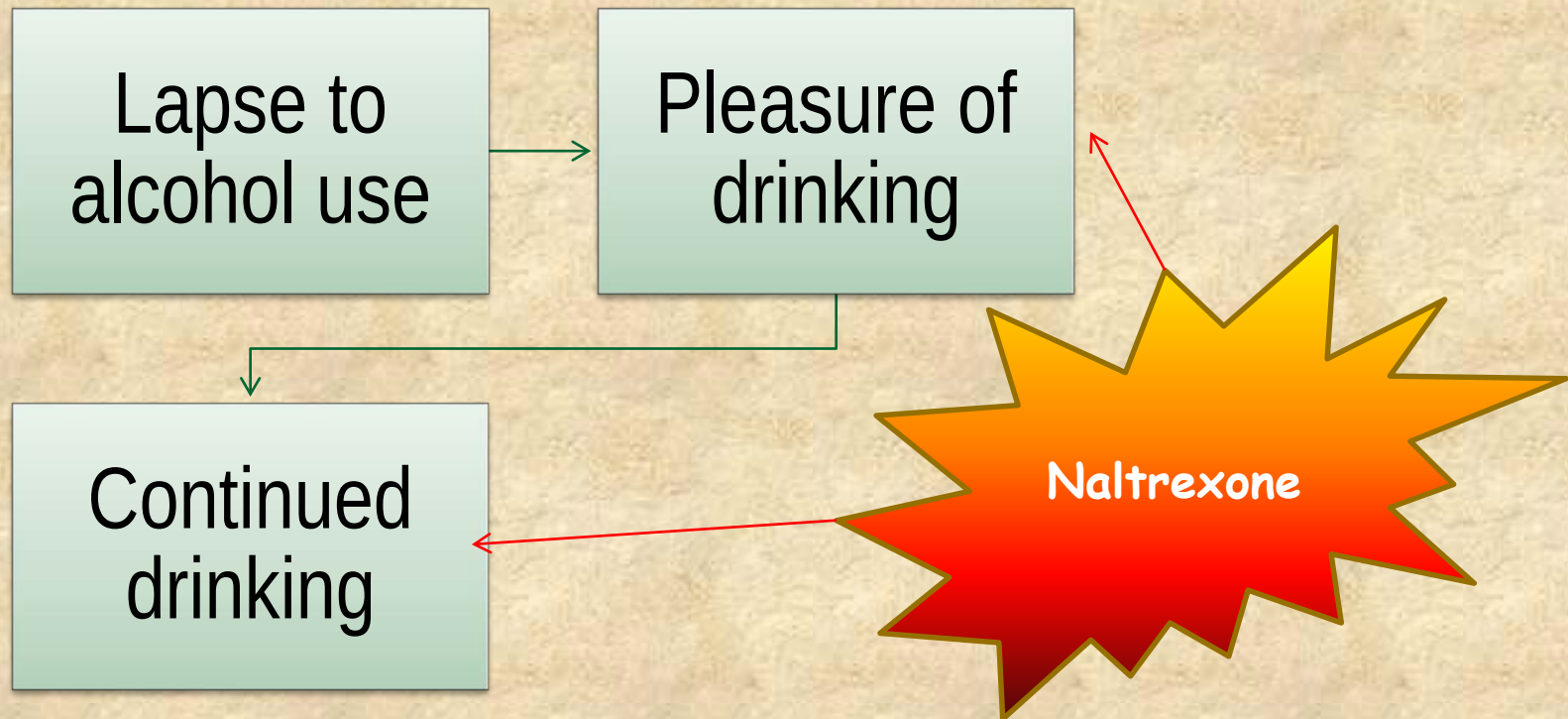
Opioid peptides mediate some of alcohol's rewarding effects



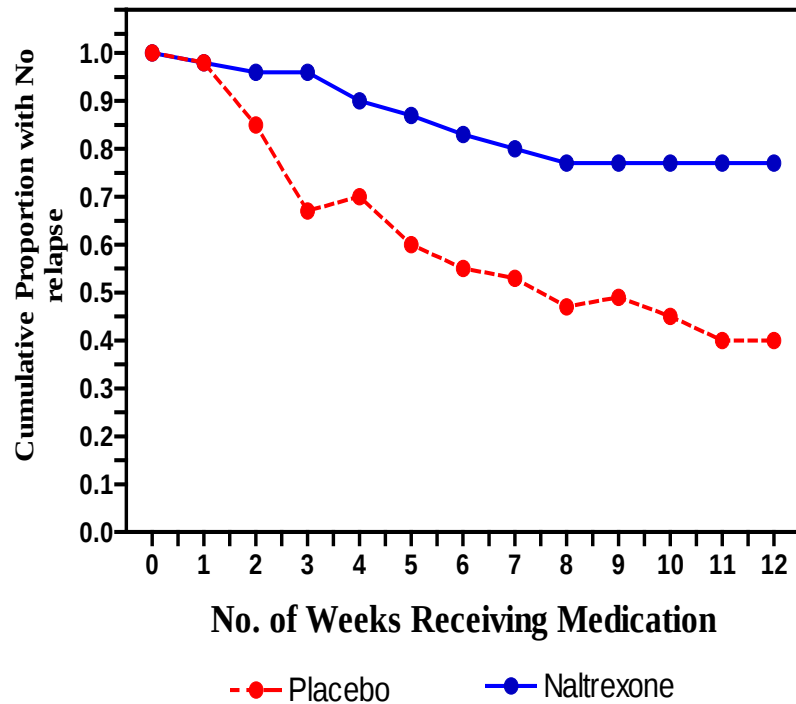
Opioid antagonists suppress alcohol-induced reward

Naltrexone: Mechanism of Action

- ❑ Reduces craving thereby reinforcement
- ❑ Thus prevents relapse



Naltrexone: Clinical science



From Volpicelli et al. 1992

- Naltrexone 50 mg/day:
- Identification of the alcoholic subgroup (those with biological risk) most responsive to naltrexone is an important scientific goal
- Genetic high-risk / FH+ individuals are more responsive to naltrexone treatment

Naltrexone: Side-Effects

- ❑ Nausea
- ❑ Headache
- ❑ Anxiety
- ❑ Sedation
- ❑ Insensitive to opioid analgesia
- ❑ Hepatotoxicity (LFT should be monitored)

Neurotransmitters and Alcohol Dependence

☐ Opioids

☐ Glutamate

☐ GABA

☐ Serotonin

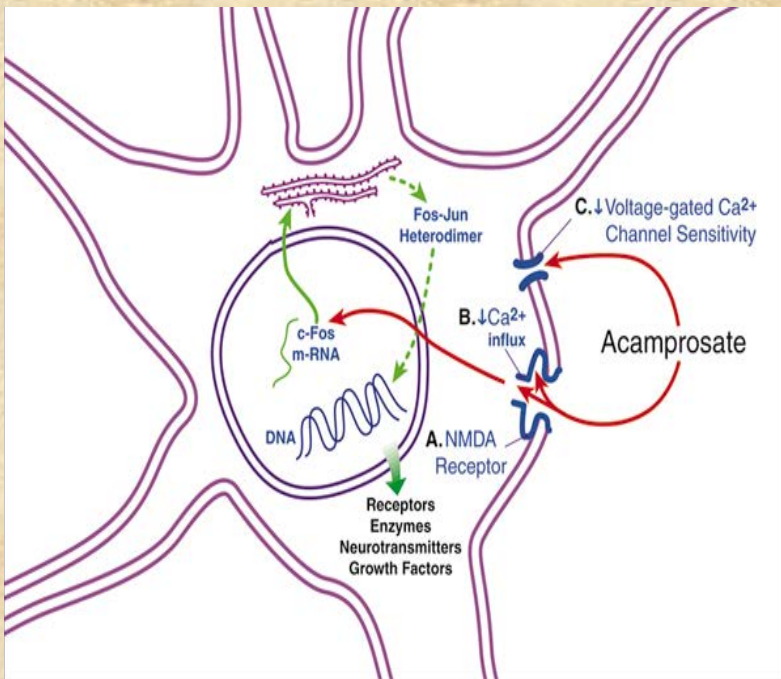
Acamprosate

Acamprosate: Advantages

- ❑ Excreted by the kidneys
- ❑ Mild side effect profile
- ❑ Good documented efficacy

Acamprosate: Basic science

- ❑ Excitatory neurotransmitter NMDA contributes to alcohol's many effects
- ❑ NMDA antagonist, acamprosate, reduces the intensity of post-cessation alcohol craving on exposure to high-risk drinking situations



Embellished from Spanagel & Ziegler, 1997

Acamprosate: Clinical science

- ❑ Poorly absorbed with a bioavailability of approx. 10%
- ❑ Excreted unmetabolized; therefore no risk of hepatotoxicity
- ❑ Should be used with caution in individuals with renal impairment
- ❑ Few adverse events; diarrhea is the most frequent
- ❑ Dose: 666 mg thrice a day
- ❑ Can be used with other alcoholism medications such as Naltrexone or Disulfiram

Neurotransmitters and Alcohol Dependence

☐ Opioids

☐ Glutamate

☐ GABA

☐ Serotonin

Baclofen

Baclofen: Clinical science

- ❑ Baclofen (p-chlorophenyl-GABA): orally active GABA-mimetic agent
- ❑ Selective GABA_B receptor agonist
- ❑ Pharmacokinetics:
 - ❑ Completely absorbed-oral administration
 - ❑ low levels of liver metabolism (about 15%),
 - ❑ Excreted unchanged in urine
 - ❑ Plasma half-life- 3-4 hours

Baclofen: Clinical science

Dosage:

Start at

- ❑ 5 mg tds for 3days, then
- ❑ 10 mg tds
- ❑ increasing as tolerated to 80-100 mg daily (maximum used- 270mg)
- ❑ Sustained release also available

Baclofen- Side effects

☐ Drowsiness

☐ Weakness

☐ Dizziness

☐ Headache

☐ Nausea

☐ Constipation

☐ Hypotension

☐ Confusion

☐ Insomnia

☐ Urinary frequency

☐ Seizures

☐ Allergic reaction

Withdrawal symptoms

☐ Hallucination

☐ Agitation

☐ Anxiety

☐ Confusion

☐ Delirium

Baclofen: role in reducing alcohol withdrawals?

- Some studies have shown that Baclofen may be useful in reducing alcohol withdrawal symptoms as well

Baclofen in reducing craving for alcohol

- ❑ Preclinical study: Animal models
 - ❑ Baclofen, suppresses the acquisition and maintenance of the alcohol drinking behavior in rats
 - ❑ Acute injection of baclofen blocked the temporary increase in voluntary alcohol intake occurring after a period of abstinence
- ❑ Clinical study: Baclofen (30 mg/day) in alcohol dependent patient
 - ❑ Reduced alcohol craving & anxiety
 - ❑ Significant reduction in the number of drinks per drinking day & number of heavy drinking days

Baclofen- Advantage

- ❑ Minimal side effect
- ❑ Showed an excellent hepatic safe profile with the lack of liver-related side effects in alcohol-dependent subjects both with and without liver cirrhosis
- ❑ Patients who continued to drink alcohol while being treated with baclofen showed no signs of any complications
- ❑ No addictive potential

Neurotransmitters and Alcohol Dependence

- ☐ Opioids
- ☐ Glutamate
- ☐ GABA
- ☐ Serotonin

Ondansetron

Ondansetron: Clinical science

- ❑ An anti-nausea agent
- ❑ Ondansetron, reduces the positive subjective effects associated with abuse liability of alcohol
- ❑ Ondansetron also reduces preference for high alcohol doses
- ❑ Dose: 4 mcg / kg/ BD
- ❑ Side effects: Malaise, fatigue, dizziness

Neurotransmitters and Alcohol Dependence

- Opioids
- Glutamate
- GABA
- Serotonin

SSRIs (Fluoxetine)

SSRIs: Clinical science

- ❑ Weak evidence of efficacy
- ❑ May be tried in patients with comorbid psychiatric illness where SSRIs are indicated

Other agent: Topiramate

- ❑ An anticonvulsant
 - ❑ Mechanism of action poorly known
 - ❑ Caution with impaired renal or hepatic function
 - ❑ Side Effects
 - ❑ psychomotor slowing, memory problems, fatigue, confusion, and somnolence.
 - ❑ Paresthesias
 - ❑ Weight loss
 - ❑ Kidney stone and Glaucoma - rare but serious
 - ❑ Decreases alcohol craving
 - ❑ Dose: initially 12.5 -25 mg once or twice a day and the total daily dose is increased by 12.5 - 25 mg every week up to 150 mg BD
-

Pharmacotherapy: Issues

- ❑ All pharmacotherapy should be combined with psychosocial interventions
 - ❑ Patient education about mech. of action, side effects, precautions, likely duration etc.
 - ❑ Relapse prevention
- ❑ Supervised therapy as far as possible
- ❑ Careful monitoring and follow-up
- ❑ Duration: 6 months to one year

Pharmacotherapy: Issues

❑ Disulfiram or Anticraving drugs: how to choose?

- Complete abstinence?
- Normal LFT?
- Supervision possible?
- Compliance assured?



Disulfiram

- Controlled drinking
- Normal LFT



Naltrexone

- Controlled drinking
- Deranged LFT



**Acamprosate /
Baclofen**

Role of combinations

- ❑ Many patients, though motivated, to stop completely, complain of craving
- ❑ Craving:
 - ❑ Can be a cause for relapse
 - ❑ Can be a distressing symptom
- ❑ Thus most patients on Disulfiram can also be put concurrently on anti-craving agents

Alcohol dependence

```
graph TD; A[Alcohol dependence] --> B[Assessment]; B --> C[Motivated ?  
Supervision possible?]; B --> D[Significant craving?]; B --> E[Motivation doubtful?  
Risk of DER?]; C --> F[Disulfiram]; D --> G[Disulfiram + anti-craving]; E --> H[Only anti-craving];
```

The flowchart outlines the treatment approach for alcohol dependence based on an initial assessment. It starts with 'Alcohol dependence' at the top, leading to an 'Assessment' stage. From the assessment, three paths emerge: 1) 'Motivated ? Supervision possible?' leads to 'Disulfiram'. 2) 'Significant craving?' leads to 'Disulfiram + anti-craving'. 3) 'Motivation doubtful? Risk of DER?' leads to 'Only anti-craving'.

Assessment

**Motivated ?
Supervision
possible?**

Disulfiram

**Significant
craving?**

**Disulfiram + anti-
craving**

**Motivation
doubtful?
Risk of DER?**

Only anti-craving



Thank You

