

PROGRESSI SCIENTIFICI, TECNOLOGICI E ORGANIZZATIVI NEI
SERVIZI PER LE DIPENDENZE: I TRATTAMENTI FARMACOLOGICI

L'impatto dei trattamenti farmacologici per l'alcolismo sui sistemi organizzativi dei servizi

Teo Vignoli



TERAPIA DELLA SINDROME D'ASTINENZA

BENZODIAZEPINE

SODIO
OXIBATO

TIAPRIDE

OFF LABEL

BACLOFENE

PREGABALIN

GABAPENTIN

TERAPIA DI MANTENIMENTO

DISULFIRAM

ACAMPROSATO

NALTREXONE

?

SODIO
OXIBATO

!

NALMEFENE

OFF LABEL

BACLOFENE

PREGABALIN

ONDANSETRON

GABAPENTIN

TOPIRAMATO

OX-
CARBAMAZEP.

**RETE
DEL
PAZIENTE**

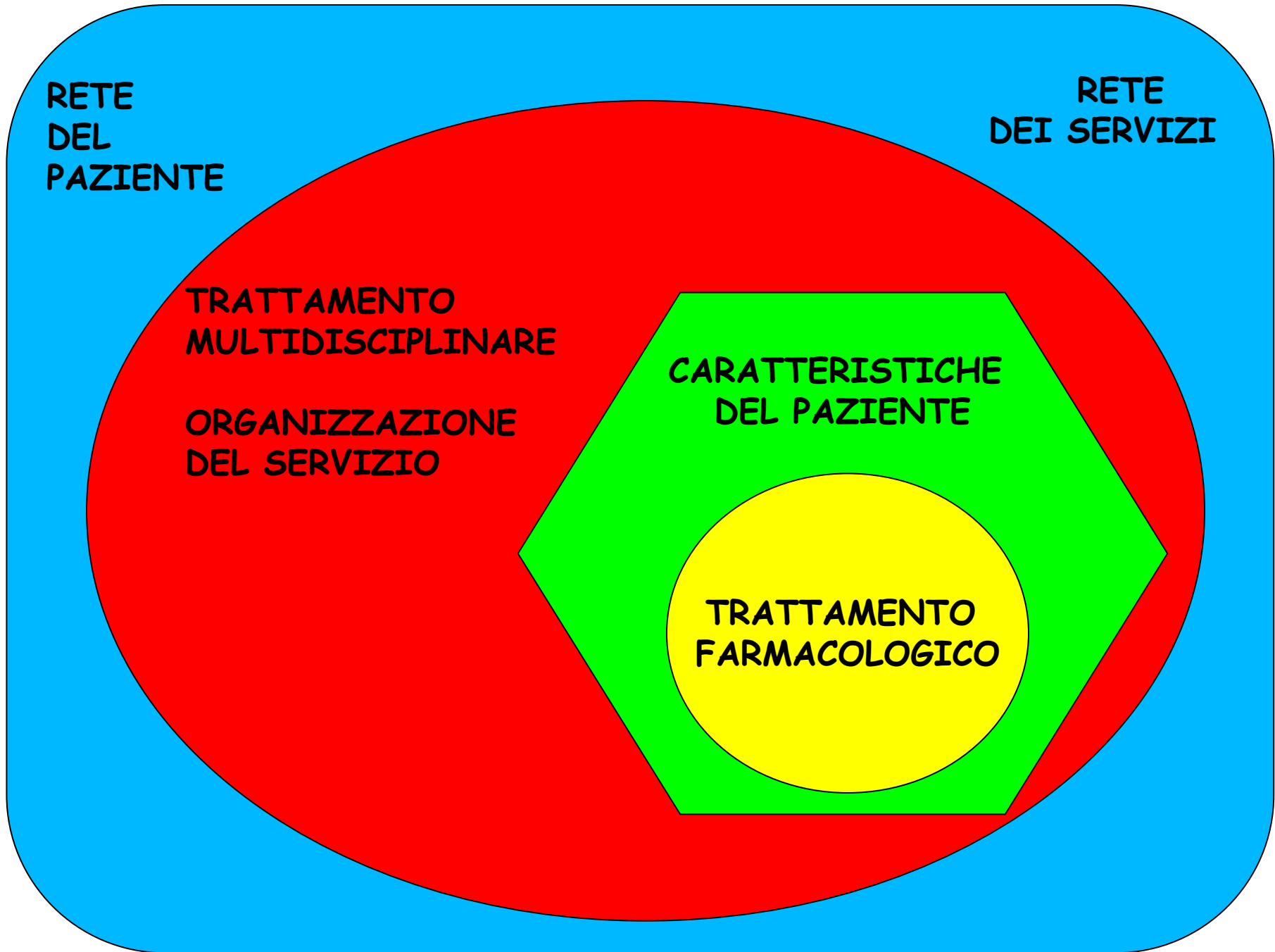
**RETE
DEI SERVIZI**

**TRATTAMENTO
MULTIDISCIPLINARE**

**ORGANIZZAZIONE
DEL SERVIZIO**

**CARATTERISTICHE
DEL PAZIENTE**

**TRATTAMENTO
FARMACOLOGICO**



COMPLICATO
CUM - PLICUM



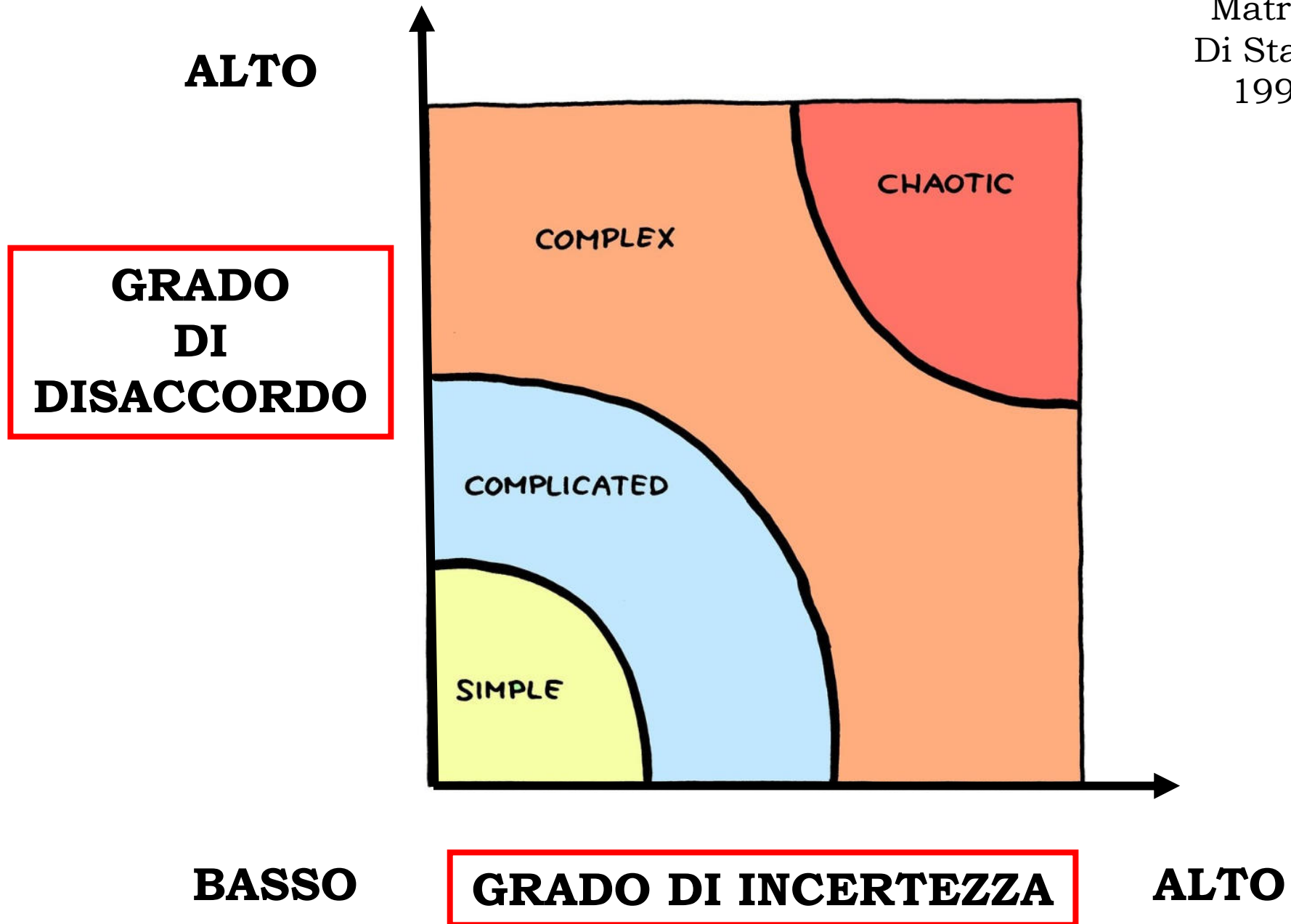
SPIEGARE

COMPLESSO
CUM - PLEXXO



COMPRENDERE

Matrice
Di Stacey
1993



TERAPIA FARMACOLOGICA DELL'ASTINENZA

Algoritmo Diagnostico e delle Procedure

LINEE GUIDA ALCOL

Centro di Riferimento Alcolologico Regione Lazio

area medica | sindrome astinenziale

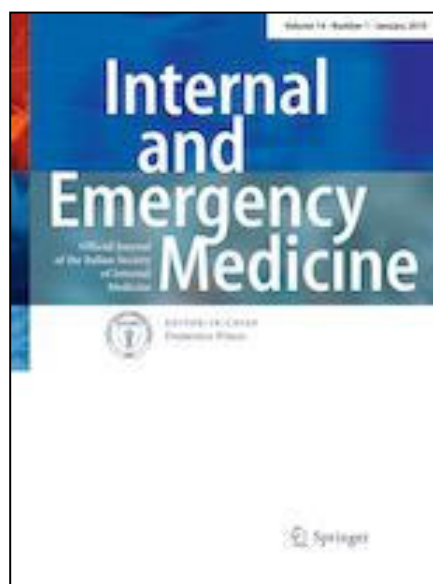
CIWA-ar < 8 (SAA Lieve)	CIWA-ar 8-15 (SAA Moderata)	CIWA-ar >15 (SAA Severa)
• ricovero non necessario • trattamento farmacologico con bdz non indicato o comunque somministrazione di bassissimi dosaggi (importante valutare anamnesi alcolica, in particolare precedenti tentativi di interruzione di assunzione di alcol) • possibilità di prescrivere farmaci per prevenzione delle ricadute	• ricovero non necessario salvo complicazioni (patologie acute o croniche, gravidanza, storia di epilessia in precedenti SAA, rischio di suicidio) • trattamento farmacologico con bdz necessario (via di somministrazione o orale)	• ricovero necessario • trattamento farmacologico con bdz endovena • somministrazione di alfa2 agonisti, beta bloccanti, neurolettici per il trattamento delle complicate (allucinazioni, crisi epilettiche)

TERAPIA FARMACOLOGICA DELL'ASTINENZA

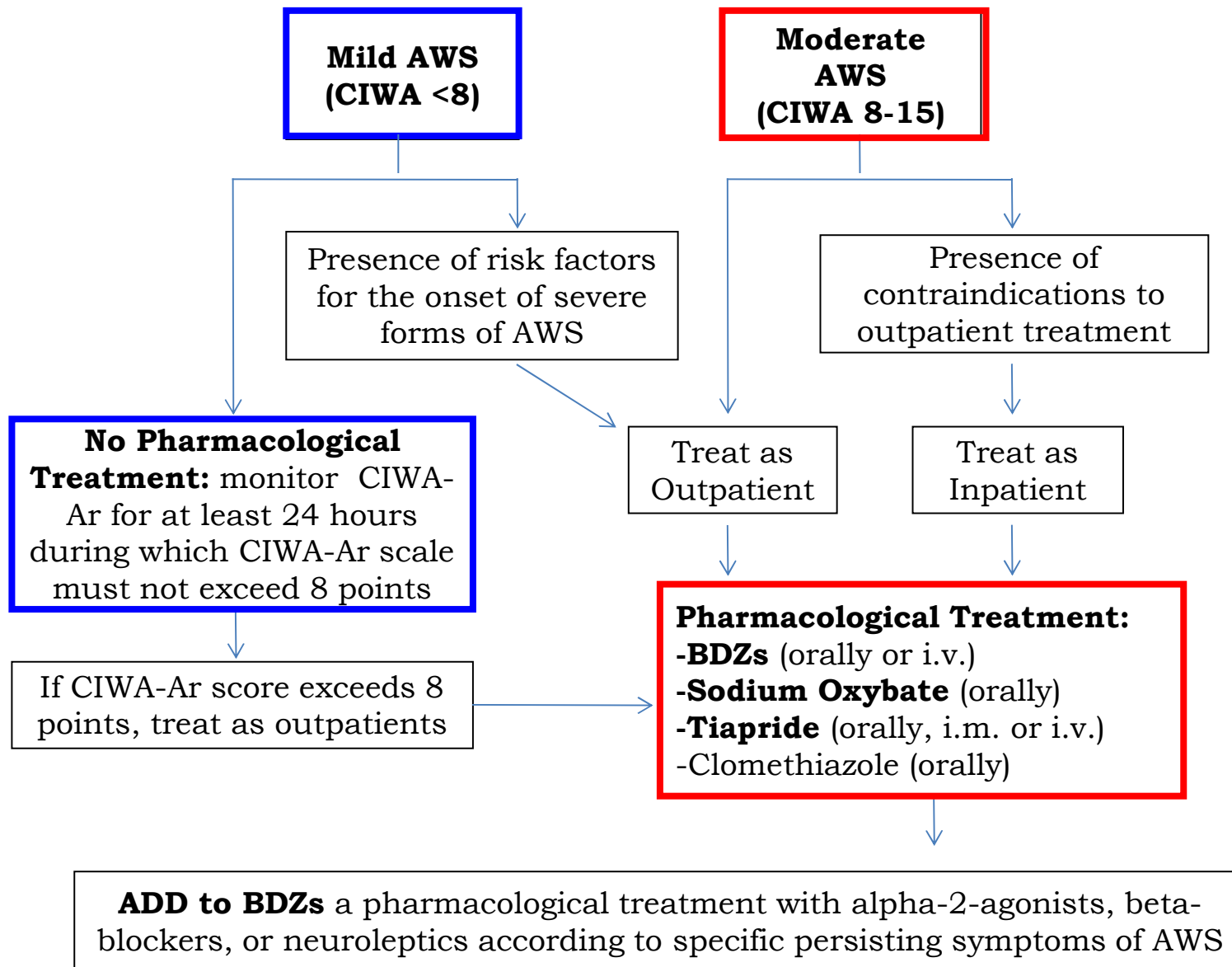
Diagnosis and treatment of acute alcohol intoxication and alcohol withdrawal syndrome: position paper of the Italian Society on Alcohol

Fabio Caputo^{1,2} · Roberta Agabio³ · Teo Vignoli⁴ · Valentino Patussi⁵ · Tiziana Fanucchi⁵ · Paolo Cimarosti⁶ · Cristina Meneguzzi⁶ · Giovanni Greco⁷ · Raffaella Rossin⁸ · Michele Parisi⁹ · Davide Mioni¹⁰ · Sarino Arico¹¹ · Vincenzo Ostillo Palmieri¹² · Valeria Zavan¹³ · Pierluigi Allosio¹⁴ · Patrizia Balbinot¹⁵ · Maria Francesca Amendola¹⁶ · Livia Macclò¹⁷ · Doda Renzetti¹⁸ · Emanuele Scafato¹⁹ · Gianni Testino¹⁵

Accepted: 22 August 2018 Internal and Emergency Medicine



Società Italiana di Alcolologia



**Severe AWS
(CIWA >15)**

**Severe AWS (CIWA >15)
complicated with DTs**

**Severe AWS (CIWA >15)
complicated with
seizures**

Treat as Inpatient

Treat as Inpatient

BDZs even at high dose i.v. in order to achieve a slightly
dozing, but still arousable state:

- Diazepam: 10 mg i.v. (every 5-10 minutes) up to a
maximum doses of 200 mg e.v. in 3 hours
- Lorazepam: 4 mg i.v. (every 15-20 minutes) up to a
maximum dose of 40 mg i.v. in 3 hours

**Use anticonvulsants in
association with BDZs:**

- carbamazepine: 800 mg/day orally
- gabapentin: 1200 mg/day orally
- valproic acid: 1200-1500 mg/day orally
- pregabalin: 450 mg/day orally
- topiramate: 100 mg/day orally
- levetiracetam: 1-2 g/day orally or i.v

In the case of refractory forms:
-admit patients to ICU
-do not discontinue BDZs
-intubation may be necessary*
-infusion of **phenobarbital** 10-15
mg/kg i.v. or i.v. boluses

In the case of refractory forms:
-intubation is strongly recommended*
-start with **propofol** induction i.v.
(100-200 mg/h) followed by propofol
i.v. infusion

In the case of resolution of
symptoms, observe patients
and plan a tapering
procedure of discontinuation
of phenobarbital and BDZs

TERAPIA FARMACOLOGICA DEL MANTENIMENTO

ACAMPROSATO

L'efficacia del farmaco è evidente nella prevenzione delle ricadute, ma non nella riduzione dei "giorni di consumo elevato di alcol" (2). RACCOMANDAZIONE A1

Algoritmo Diagnostico e delle Procedure

LINEE GUIDA

NALTREXONE

Nei soggetti con polimorfismo genetico G del gene che codifica il recettore per gli oppioidi Mu (OPRM1) (ove sia possibile eseguire questo esame): la risposta al NTX sarebbe più efficiente a dosaggi di 100 mg/die (11) (v. capitolo dedicato alla farmacogenetica). RACCOMANDAZIONE A1

Centro di Riferimento A

Il farmaco non deve essere somministrato nei pazienti con storia recente di abuso di oppioidi o utilizzo di farmaci oppioidi, con grave insufficienza renale o epatica e recenti episodi di SAA complicate da crisi epilettiche o allucinazioni. (16,17). RACCOMADAZIONE A2

DISULFIRAM

La somministrazione è consigliata sotto la supervisione di un familiare o figura di riferimento. Le controindicazioni e la non facile maneggevolezza dal punto di vista della sicurezza ne limitano fortemente l'utilizzo. (18,19) RACCOMANDAZIONE A2

SODIO OXIBATO

Necessario, quindi, realizzare studi randomizzati di buona qualità (alcuni sono in corso), con una dimensione campionaria elevate ed utilizzando scale di valutazione omogenee per avere dati validi. Inoltre va monitorizzato il rischio di abuso in pazienti poliabusatori e nella doppia diagnosi. (28-30). RACCOMANDAZIONE B2

LINEE GUIDA INTERNAZIONALI

ALCOHOL-USE DISORDERS

THE NICE GUIDELINE ON DIAGNOSIS,
ASSESSMENT AND MANAGEMENT OF
HARMFUL DRINKING AND ALCOHOL
DEPENDENCE

BMJ

2014

7.15.1 Recommendations

Interventions for moderate and severe alcohol dependence after successful withdrawal

- 7.15.1.1 After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone⁴⁵ in combination with an individual psychological intervention (cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) focused specifically on alcohol misuse (see 6.23.1.15–6.23.1.17).
- 7.15.1.2 After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone⁴⁴ in combination with behavioural couples therapy to service users who have a regular partner and whose partner is willing to participate in treatment (see 6.23.1.18).
- 7.15.1.3 After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering disulfiram⁴⁶ in combination with a psychological intervention to service users who:
- have a goal of abstinence but for whom acamprosate and oral naltrexone are not suitable, or
 - prefer disulfiram and understand the relative risks of taking the drug (see 7.15.1.18).

THE AMERICAN PSYCHIATRIC ASSOCIATION

PRACTICE GUIDELINE

FOR THE

Pharmacological Treatment of Patients With Alcohol Use Disorder

Published Online:5

Jan 2018

APA *recommends (1B)* that naltrexone or acamprosate be offered to patients with moderate to severe alcohol use disorder who

APA *suggests (2C)* that disulfiram be offered to patients with moderate to severe alcohol use disorder who

APA *suggests (2C)* that topiramate or gabapentin be offered to patients with moderate to severe alcohol use disorder who

- have a goal of reducing alcohol consumption or achieving abstinence,
- prefer topiramate or gabapentin or are intolerant to or have not responded to naltrexone and acamprosate, and
- have no contraindications to the use of these medications.

LINEE GUIDA INTERNAZIONALI

CLINICAL GUIDELINES

CNS Neuroscience & Therapeutics

Pharmacotherapy for Alcohol Dependence: The 2015 Recommendations of the French Alcohol Society, Issued in Partnership with the European Federation of Addiction Societies

Benjamin Rolland,^{1,2} François Paille,^{1,3} Claudine Gillet,^{1,4} Alain Rigaud,^{1,5,6} Romain Moirand,^{1,7,8} Corine Dano,^{1,9} Maurice Dematteis,^{1,10} Karl Mann^{11,12} & Henri-Jean Aubin^{1,12,13}

CNS Neuroscience & Therapeutics **22** (2016) 25–37

Table 5 Recommendations issued on the management of abstinence maintenance (question 12 of the GPRs)

#	Recommendation	Grade
12.4	Medications for relapse prevention should be automatically associated with adapted psychosocial support in patients with alcohol-dependence	A
12.5	Increased compliance with medications improves therapeutic efficacy	EC
12.6	<u>Acamprosate or naltrexone are the first-line treatment for supporting relapse prevention</u>	A
12.7	<u>Disulfiram can be proposed as second-line treatment</u> in patients motivated to sustain abstinence, correctly informed of the risk of the antabuse effect, and adequately supervised	EC
12.8	<u>The second-line prescription of baclofen for preventing relapse</u> among alcohol-dependent patients has been authorized by a “temporary recommendation for use” (TRU) up to the dose of 300 mg/day, and requires the online	EC

Table 6 Recommendations issued regarding the use of a drinking reduction strategy (question 10 of the GPRs)

#	Recommendation	Grade
10.1	Reducing consumption can be directly proposed to patients with mild dependence, or to patients with a more severe disorder who do not wish or are not yet able to attempt abstinence	EC
10.2	It is recommended that consumption below the at-risk levels be targeted insofar as possible, although any lasting reduction in consumption should be accepted as a positive result, and may be an initial step towards a greater reduction	EC
10.3	Self assessment of daily alcohol consumptions should be used in psychosocial support for drinking reduction	A
10.4	Medications for reducing alcohol consumption are only indicated in dependent individuals	EC
10.5	<u>Nalmefene is indicated as a first-line treatment for reducing alcohol consumption in dependent individuals</u>	A
10.6	<u>The second-line prescription of baclofen for reducing alcohol use</u> among alcohol-dependent patients has been authorized by a TRU up to the dose of 300 mg/day, and requires the online reporting of patients’ follow-up on the TRU portal	EC

LINEE GUIDA INTERNAZIONALI

Guidelines for biological treatment of substance use and related disorders, part 1: Alcoholism, first revision

Michael Soyka, Henry R. Kranzler, Victor Hesselbrock, Siegfried Kasper, Jochen Mutschler, Hans-Jürgen Möller & The WFSBP Task Force on Treatment Guidelines for Substance Use Disorders

THE WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY, 2017
VOL. 18, NO. 2, 86–119

Acamprosate has been studied in more than 5,000 alcohol-dependent patients in RCTs in 14 different countries (Rösner et al. 2010a; Maisel et al. 2013; Jonas et al. 2014). The drug significantly reduced relapse rates in alcohol-dependent patients in a number of RCTs (see Table 2) (*Level A, RG1*). Meta-analyses pro-

Taken together, because of side effects, including the potentially dangerous DAR, and poor adherence, disulfiram is best considered a second-line medication in relapse prevention (*Level B, RG3*). However, in severely affected patients, supervised disulfiram treatment is a treatment option with a good effect size.

In conclusion, there is abundant evidence supporting the use of oral naltrexone for treating alcohol dependence (*Level A, RG1*). However, the optimal dosage and duration of treatment are two important clinical questions that remain to be adequately addressed, along with the most appropriate patient population and optimal treatment goal (i.e., harm reduction/reduction of heavy drinking days vs. abstinence).

Diagnosis and Pharmacotherapy of Alcohol Use Disorder: A Review (Kranzler & Soyka, JAMA, 2018)

	Medication ^a			
	Disulfiram	Naltrexone	Long-Acting Injectable Naltrexone	Acamprosate
Indication	Management of selected chronic alcohol patients who want to remain in a state of enforced sobriety	Treatment of alcohol dependence	Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting	Maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent
Dosage	FDA-approved dosage: 250-500 mg/d orally	FDA-approved dosage: 50 mg/d orally	FDA-approved dosage: 380 mg/mo intramuscularly	FDA-approved dosage: 1998 mg/d orally
	Dosage used in clinical trials: 125-500 mg/d	Dosage used in clinical trials: 50-100 mg/d, with an initial dosage of 25-50 mg/d	Dosage used in clinical trials: 190 mg or 380 mg/mo	Dosage used in clinical trials: 1000-3000 mg/d
Effect size(s)	A meta-analysis of 22 studies (N = 2414)¹³ showed an association of disulfiram with sustained abstinence from alcohol compared to control conditions only in open-label studies (Hedges g = 0.70, 95% CI, 0.46 to 0.93); there was not a significant association in blinded trials (Hedges g = 0.01, 95% CI, -0.29 to 0.32).^b Disulfiram was associated with a better response than control conditions when medication adherence was supervised (N = 13 studies; Hedges g = 0.82, 95% CI, 0.59 to 1.05), but not when it was unsupervised (N = 9 studies; Hedges g = 0.26, 95% CI, -0.02 to 0.53).¹³	A meta-analysis (N = 16 studies and 2347 patients) showed a risk decrease (RD) for a return to any drinking associated with naltrexone 50 mg/d (RD = -0.05 (95% CI, -0.10 to -0.002); number needed to treat (NNT) = 201). Naltrexone was also associated with reduced risk of binge drinking (19 studies; N = 2875; RD = -0.09 (95% CI, -0.15 to -0.04); NNT = 12).¹¹	In the only placebo-controlled trial of long-acting naltrexone, the median monthly number of binge drinking days declined by 13.3 in the placebo group (to 6.0/mo), 14.8 in the 190-mg group (to 4.5/mo), and 16.2 in the 380-mg group (to 3.1/mo).²⁰	In a meta-analysis of 16 studies (N = 4827),¹¹ acamprosate treatment was associated with a greater reduction in the risk of drinking among abstinent patients (RD = -0.09 (95% CI, -0.14 to -0.04); NNT = 12), but no reduction in the likelihood of binge drinking.

SODIO OXIBATO ?

Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses (Review)

Leone MA, Vigna-Taglianti F, Avanzi G, Brambilla R, Faggiano F



Authors' conclusions

GHB 50mg is effective compared to placebo in the treatment of AWS, and in preventing relapses in previously detoxified alcoholics at 3 months follow-up, but the results of this review do not provide sufficient evidence in favour of GHB compared to benzodiazepines and Chlormethiazole for AWS prevention. GHB is better than NTX and Disulfiram in maintaining abstinence and it has a better effect on craving than placebo and Disulfiram. Side effects of GHB are not statistically different from those with BZD, NTX or Disulfiram. However, concern has been raised regarding the risk of developing addiction, misuse or abuse, especially in polydrug abusers.

SODIO OXIBATO ?

Incidence of abuse/misuse, central nervous system depression and dependence to sodium oxybate in alcohol-dependent patients

<i>Number of events (incidence)</i>	<i>Clinical trials, N = 3436</i>	<i>Pharmacovigilance database, N = 260 000</i>
Abuse/misuse	100 (2.91%)	6 (0.002%)
CNS depression	19 (0.55%)	14 (0.005%)
Dependence/withdrawal	4 (0.12%)	2 (0.001%)

(Alcover Assessment Report, EMA/833636/201, 2017)

Importantly, no deaths attributable to the use of sodium oxybate have ever been reported in the pharmacovigilance database or in the clinical database

Article highlights

- Safety data showed that SMO has a good safety profile in alcohol-dependent patients regardless of the DRL prior to treatment; such a good safety profile was confirmed by pharmacovigilance data for Alcover®.
- Adverse events are transitory and do not require discontinuation of treatment, and no side effects due to the combination of alcohol and SMO have been found in those patients who were still drinking during the treatment
- Very rare cases of SMO abuse and dependence may occur during treatment; patients with psychiatric comorbidities (particularly those with borderline personality disorder) or who are in remission from cocaine or heroin addiction have an increased risk of SMO abuse and caution is required when SMO therapy is contemplated in these patients (a controlled dispensing is required).

This box summarizes key points contained in the article.

SODIO OXIBATO ?

Sindrome da astinenza protratta da alcol:
il ruolo del sodio ossibato...e non solo

MDD 37 - Marzo 2020

di Fabio Caputo, Teo Vignoli, Mauro Cibiñ, Roberto De Giorgio e Giorgio Zoli

Newsletter “Clinica dell’Alcolismo”

Anno VII, n. 29

MISSION n. 53

La sindrome da astinenza alcolica protratta

a cura di Alfio Lucchini*

The recognition and management of
protracted alcohol withdrawal may
improve and modulate the pharmacological
treatment of alcohol use disorder

Fabio Caputo^{1,2}, Mauro Cibiñ³, Antonella Loche⁴,
Roberto De Giorgio⁵ and Giorgio Zoli⁵



Journal of Psychopharmacology
2020, Vol. 34(11) 1171–1175
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SAGE

Substance Abuse Treatment

ADVISORY
News for the Treatment Field

PROTRACTED WITHDRAWAL

July 2010
Volume 9
Issue 1

La SAP è definita come la presenza di segni e sintomi sostanza-specifici persistenti tipici della sindrome astinenziale acuta. I sintomi della SAP includono ansia, ostilità, irritabilità, depressione, instabilità del tono dell’umore, astenia, insonnia, difficoltà di concentrazione, riduzione della libido, sensazione di fastidio fisico o dolore non imputabile ad altre cause.

Considerando che i sintomi della SAP sono conseguenti ai neuroadattamenti dei sintomi GABA e NMDA causati dal consumo cronico di alcol, è evidente. Quindi, dopo il superamento delle prime fasi della SAA, il proseguimento della terapia con sodio ossibato, continuata ulteriormente per almeno 3-6 mesi al fine di modulare il più possibile i sintomi della SAP, trova una indicazione razionale.

DISULFIRAM ?

OPEN ACCESS Freely available online

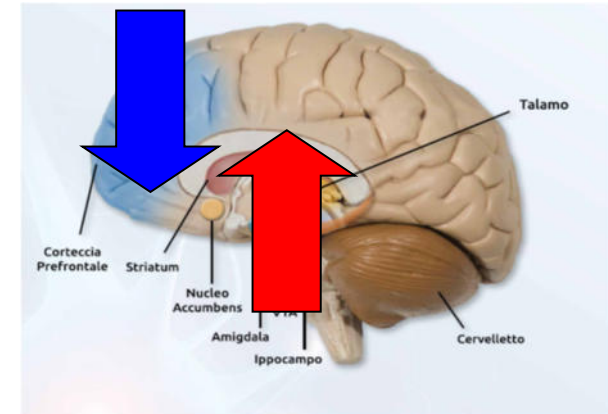
PLOS ONE

Disulfiram Efficacy in the Treatment of Alcohol Dependence: A Meta-Analysis

Marilyn D. Skinner^{1*}, Pierre Lahmek², H  lo  se Pham³, Henri-Jean Aubin⁴

¹ Centre de Traitement des Addictions, H  pital Emile Roux, Assistance Publique-H  pitaux de Paris, Institut National de la Sant   et de la Recherche M  dicale U669, Limeil-Br  vannes, France, ² Centre de Traitement des Addictions, H  pital Emile Roux, Assistance Publique-H  pitaux de Paris, Limeil-Br  vannes, France, ³ Centre M  dical Marmottan Paris, France, ⁴ Centre d'Enseignement, de Recherche et de Traitement des Addictions, H  pital Paul Brousse, Assistance Publique-H  pitaux de Paris, Universit   Paris-Sud, Institut National de la Sant   et de la Recherche M  dicale U669, Villejuif, France

Conclusions: Blinded studies were incapable of distinguishing a difference between treatment groups and thus are incompatible with disulfiram research. Based on results with open-label studies, disulfiram is a safe and efficacious treatment compared to other abstinence supportive pharmacological treatments or to no disulfiram in supervised studies for problems of alcohol abuse or dependence.



Anticipazione
conseguenze delle azioni
Delay discount
Inibizione del
comportamento

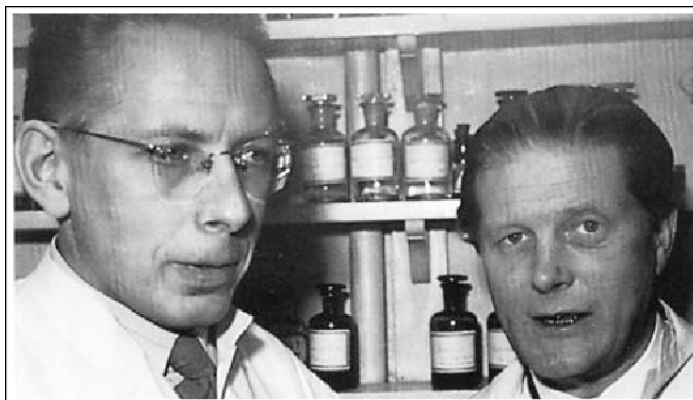


Figure 1. Jacobsen (right) and Hald in Medicinalco's

Approccio
anni '50

Condizionamento
avversivante

Approccio
contemporaneo

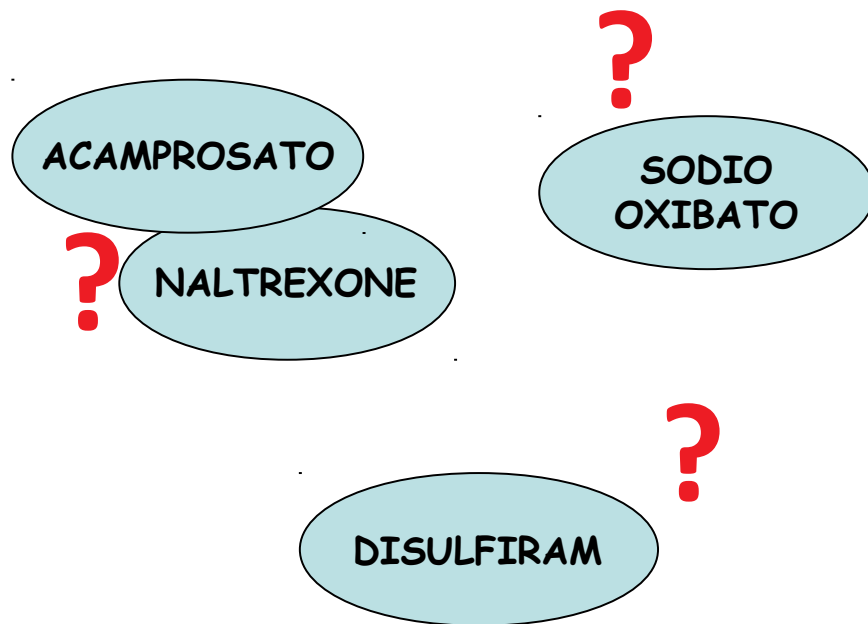
Potenziamento
cognitivo

IL CASO DEL BACLOFENE!

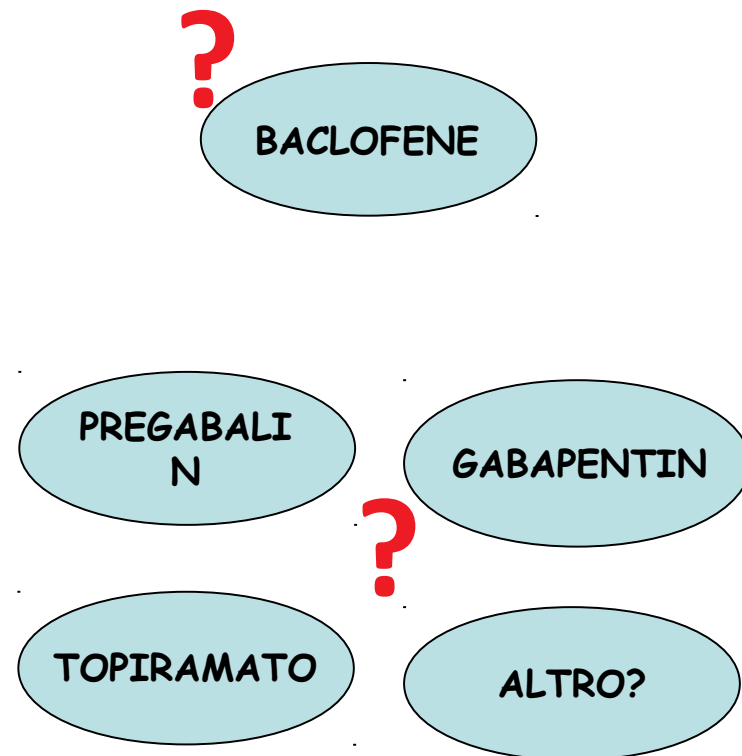
EASL Clinical Practice Guidelines: Management of alcohol-related liver disease[☆]

with ALD. Some studies suggest that baclofen, a GABA-B receptor agonist, increases abstinence rate and prevents relapse in alcohol-dependent patients.⁶³ Moreover, to date, baclofen represents the only alcohol pharmacotherapy tested in patients with AUD, with significant liver disease. A clinical trial demonstrated the safety and efficacy of baclofen in promoting alcohol abstinence in patients with ALD and cirrhosis,⁶⁴ but confirmatory studies in cirrhotic patients are warranted, since a recent trial in patients with hepatitis C virus (HCV) did not show any superiority of 30 mg of baclofen over placebo.⁶⁵ Studies with

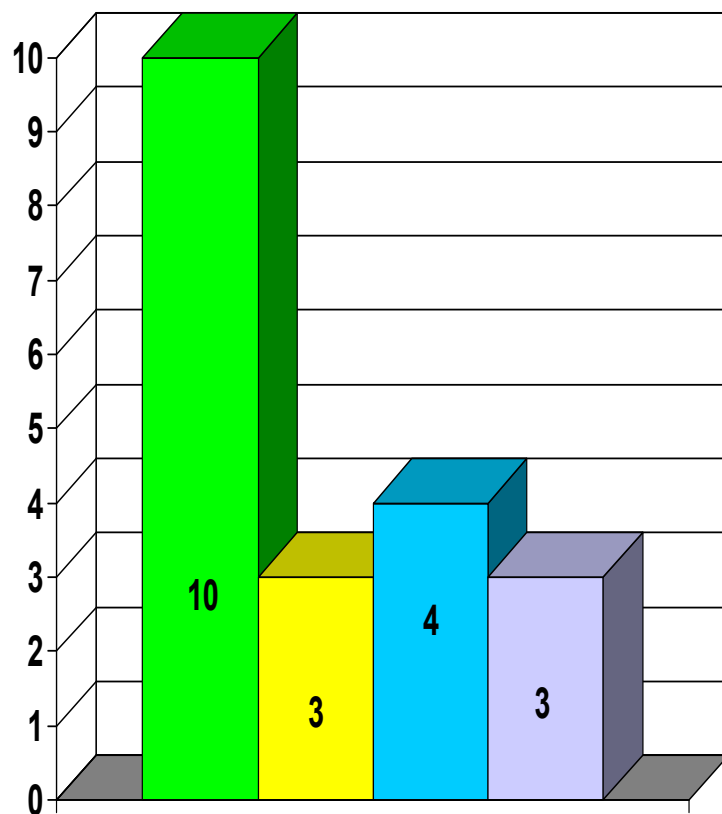
CHE GRADO DI CERTEZZA CI DANNO LE LINEE GUIDA?



OFF LABEL

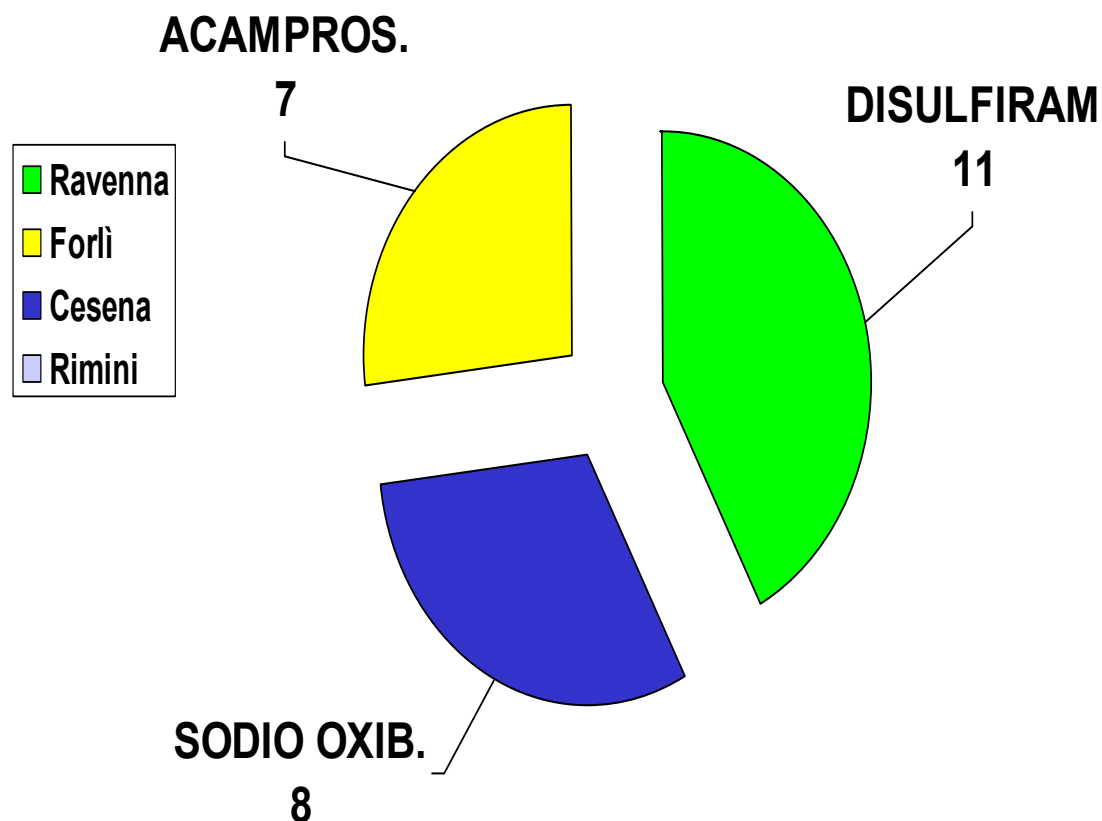


Questionario anonimo ai prescrittori dei SerDP della AUSL Romagna

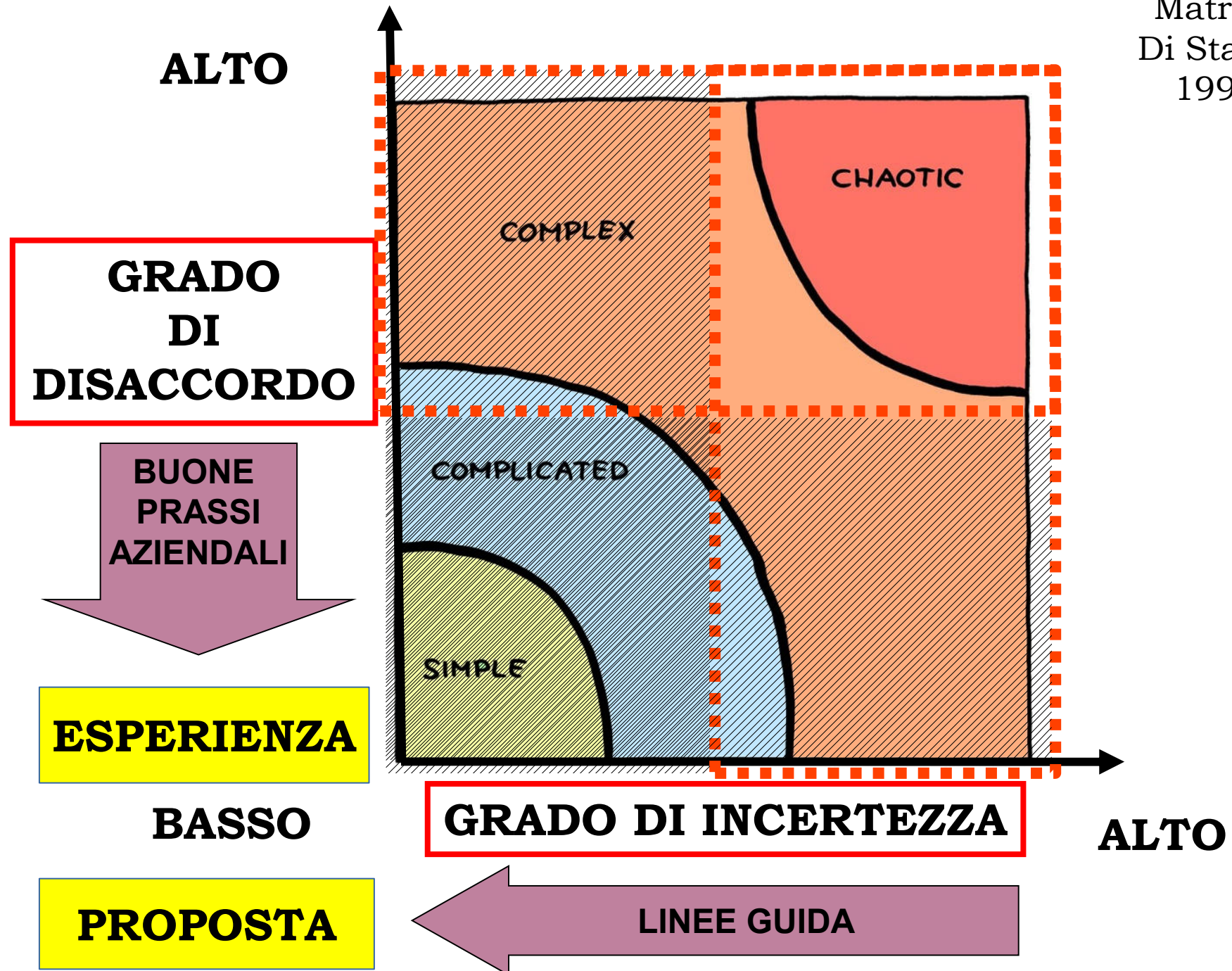


Medici prescrittori che hanno
eseguito il questionario

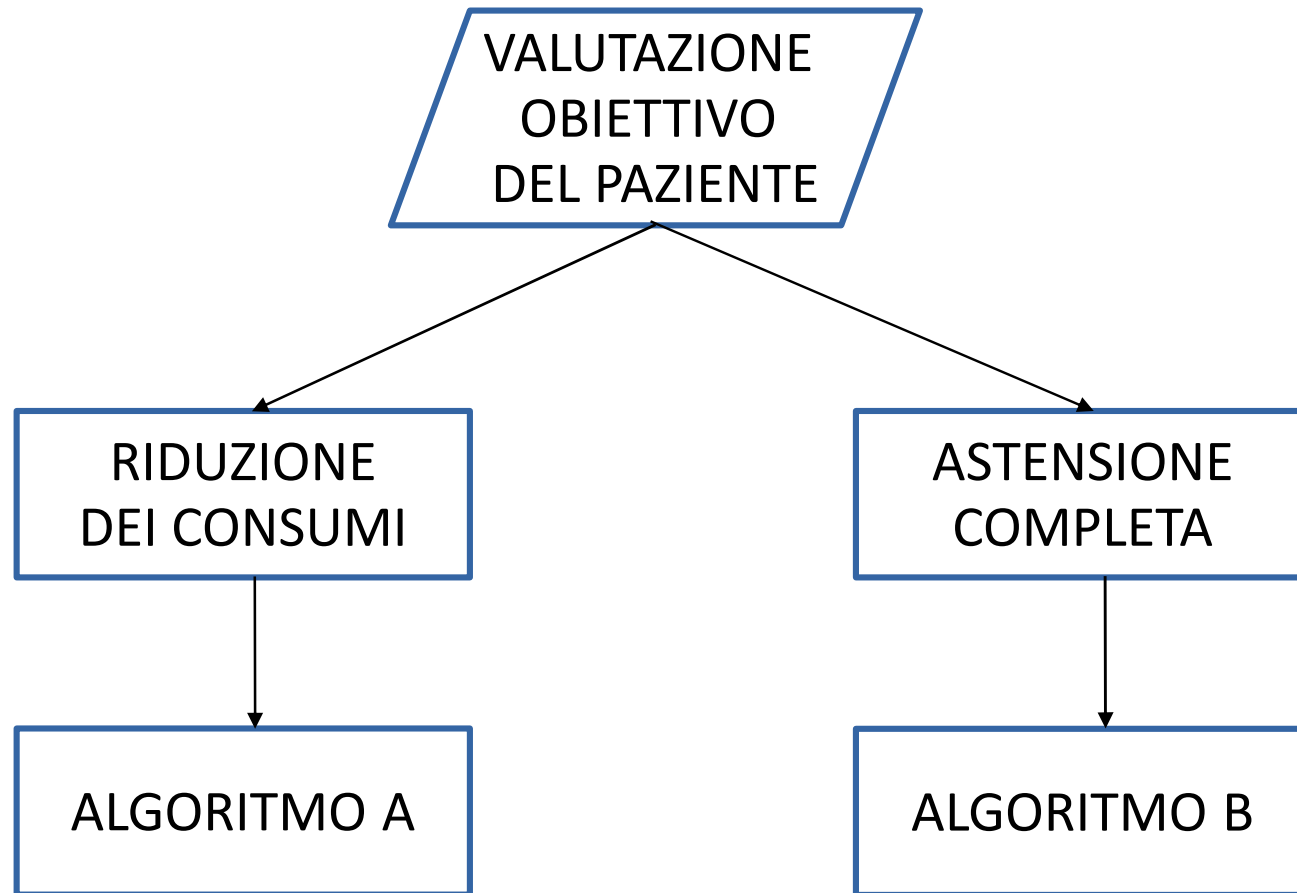
D1- Quale farmaco usi con
maggiore frequenza?

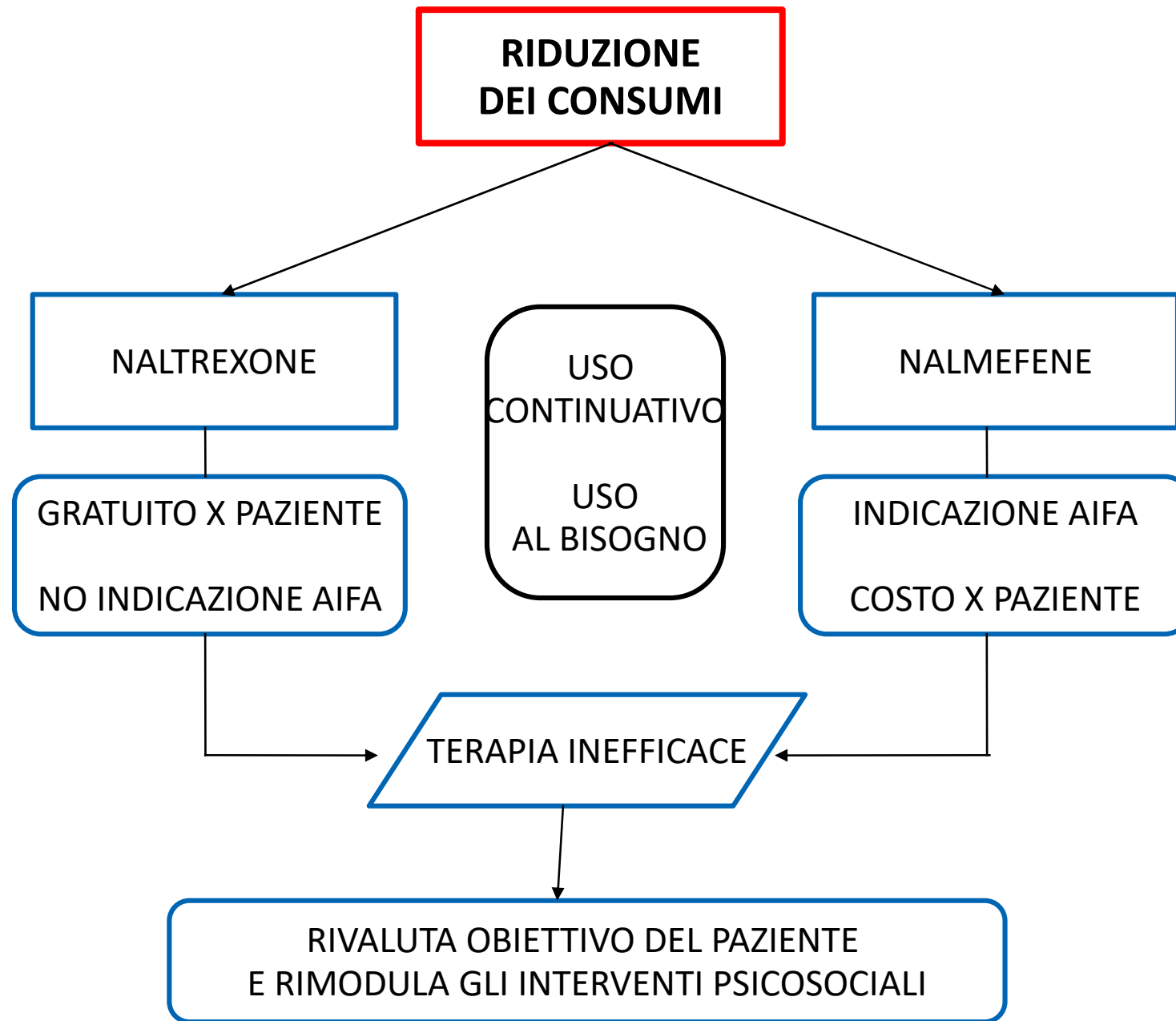


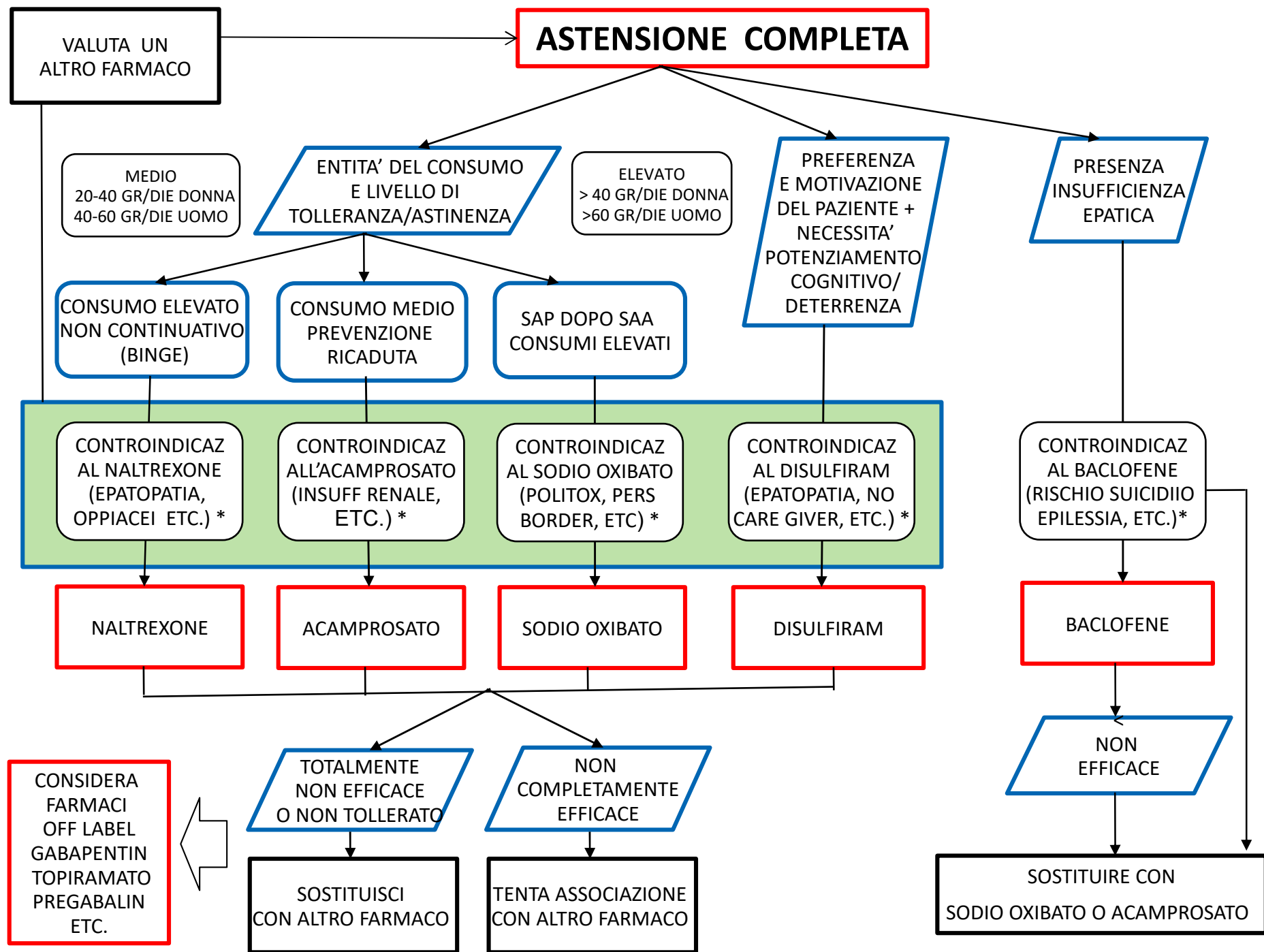
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Di Stacey
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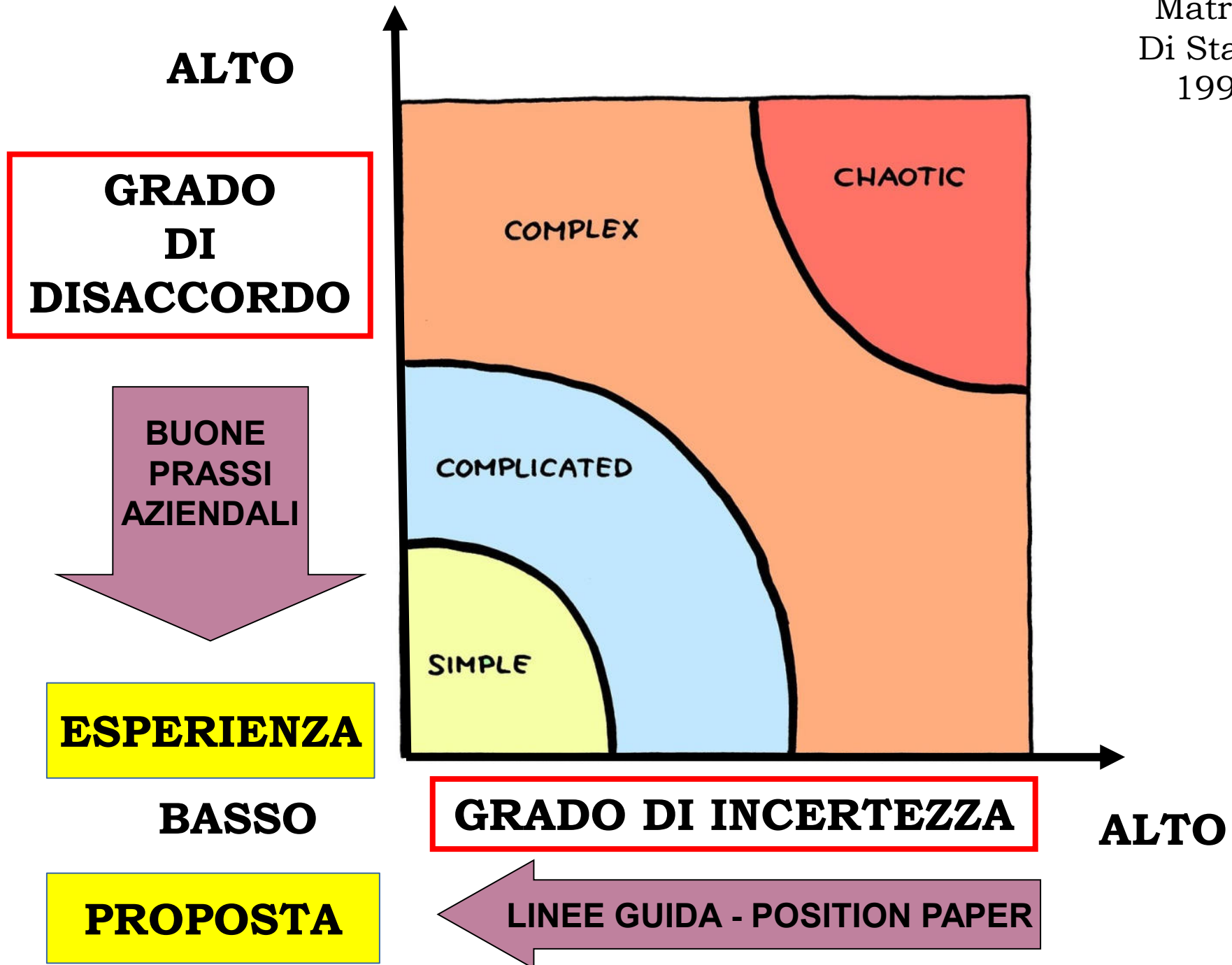


DIAGNOSI DI DISTURBO DA USO DI ALCOL
DI GRADO MODERATO O SEVERO









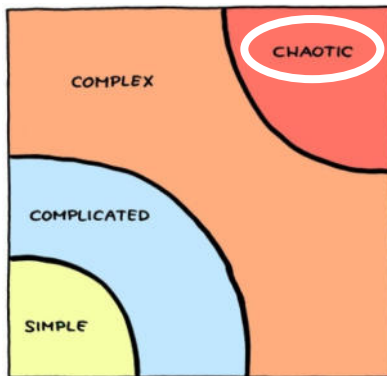
BUDGET

Ridefinizione degli
obiettivi di Budget

Disomogeneità
prescrittiva di
farmaci costosi

**BOTTOM
UP**

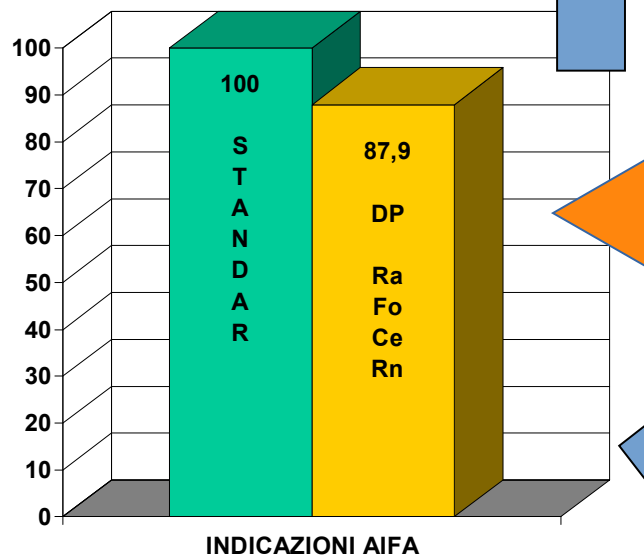
Linee di indirizzo
aziendali/locali - PDTA



**TOP
DOWN**

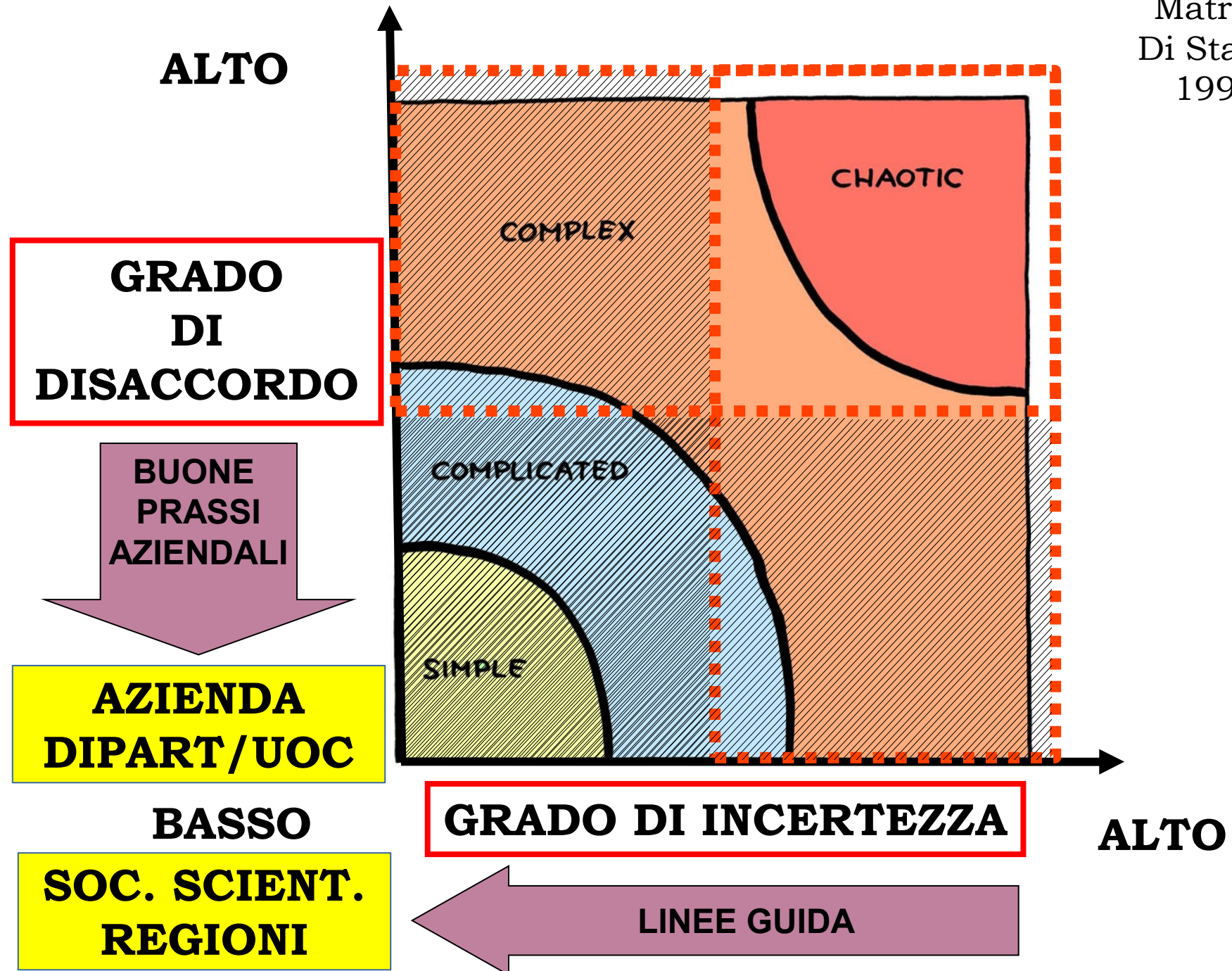
AUDIT

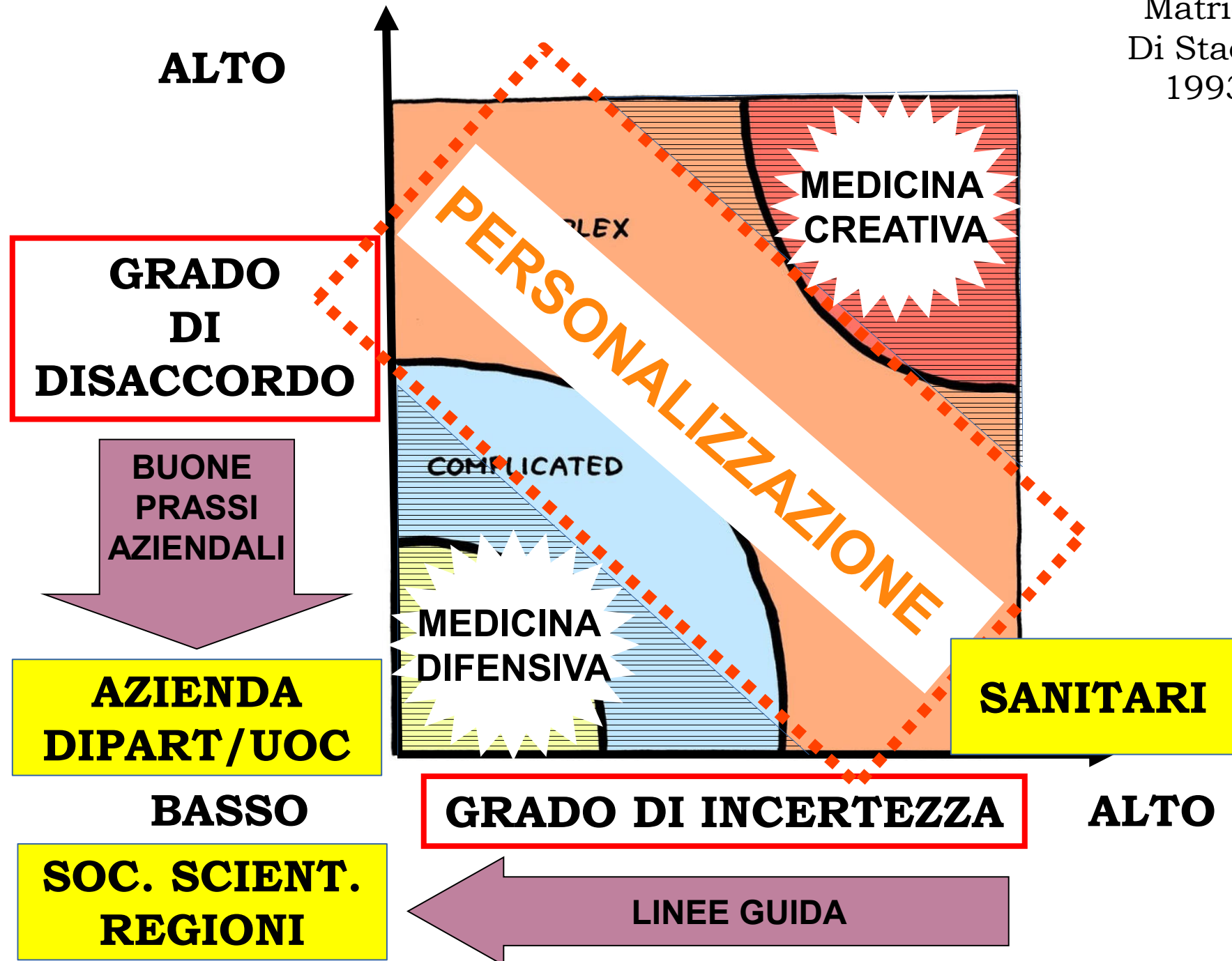
Adeguarsi alla media o al
minimo (efficiency)



**DISOMOGENEI
E APPROPRIATI**

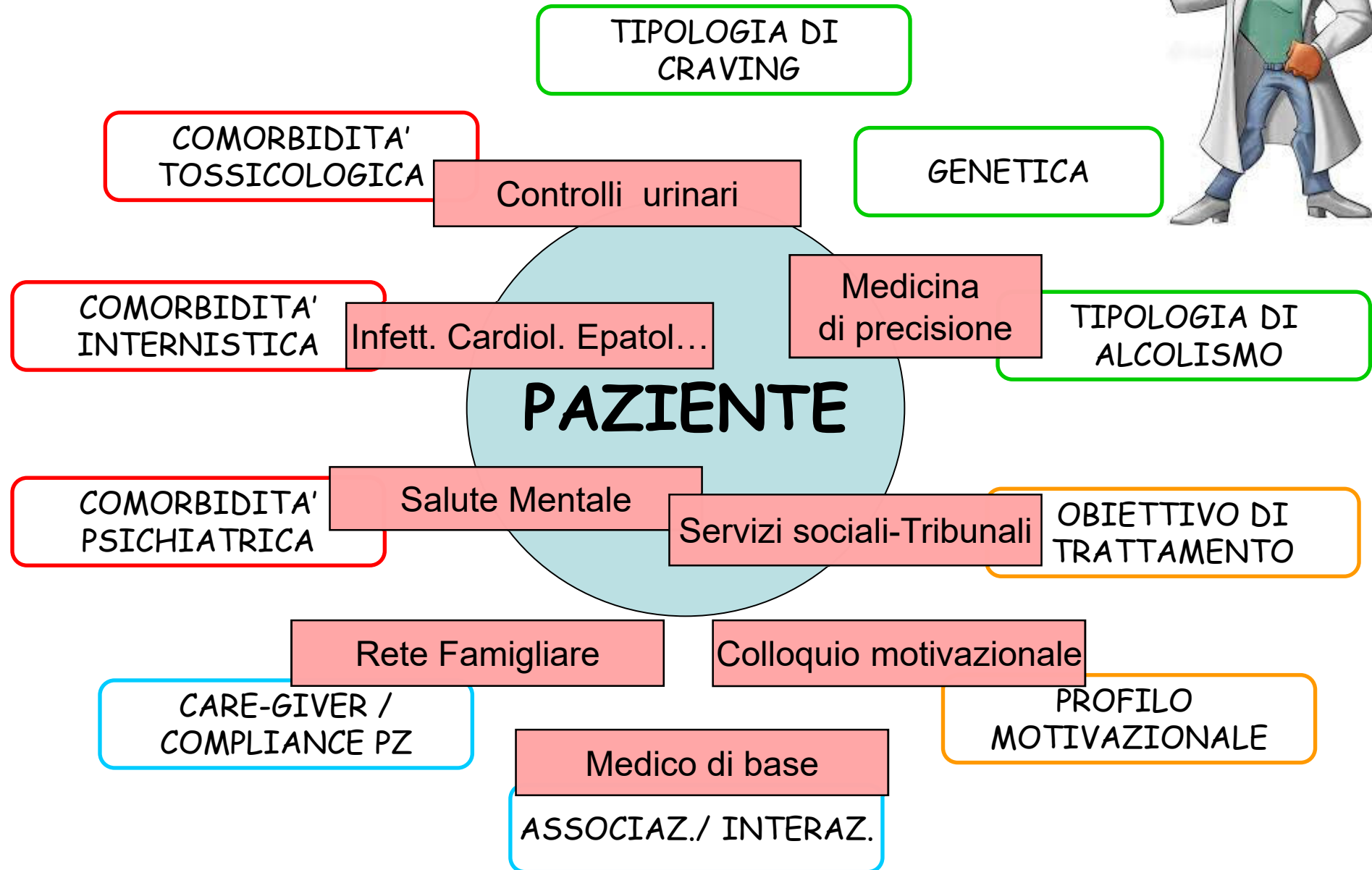
Matrice
Di Stacey
1993





PERSONALIZZAZIONE DEI TRATTAMENTI

Vignoli, Caputo - Alcologia 25/26/27 - 30-42



Take Home Messages

SOCIETA' SCIENTIFICHE:

Necessità di Consensus Conference
Linee Guida Italiane per aumentare le
certezze

AZIENDE SANITARIE:

Necessità di linee di indirizzo - buone
prassi prescrittive locali per aumentare
il livello di accordo

PROFESSIONISTI:

Accettare la sfida della complessità
significa NON semplificare e
accettare decisioni condivise

