



La Polifarmacoterapia nell'addiction: interazioni farmacologiche, monitoraggio degli eventi avversi, complessità della gestione

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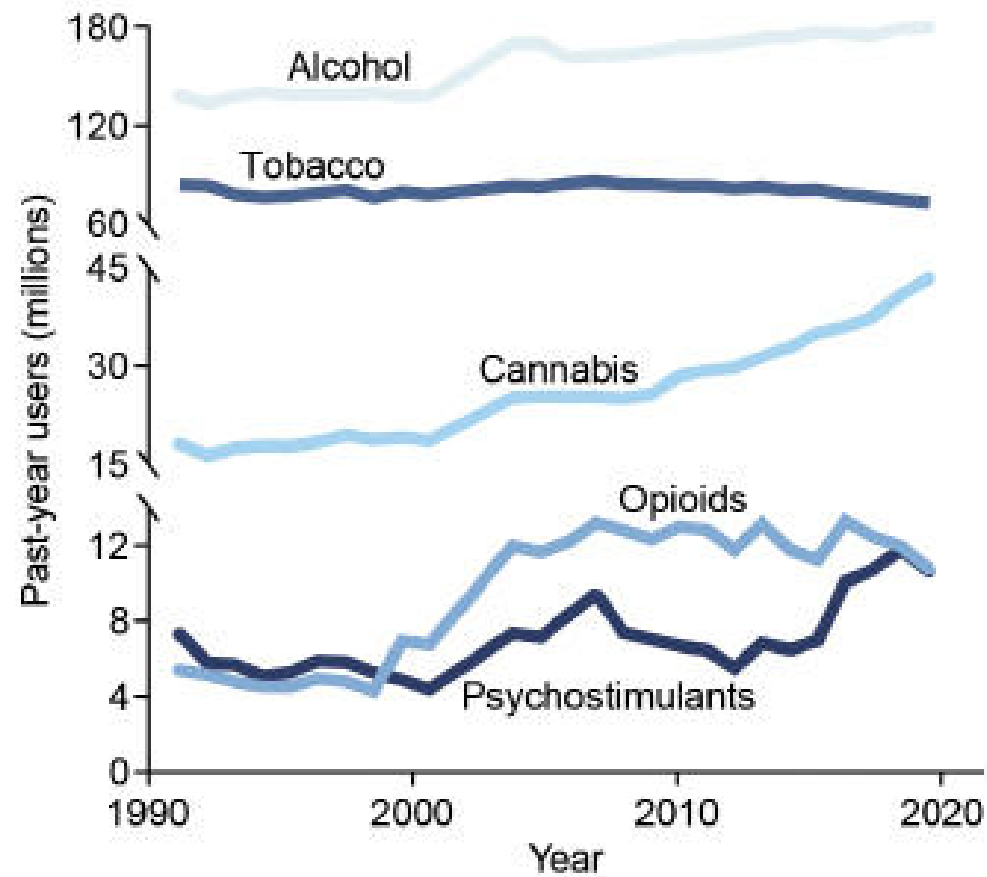
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Perchè parlare di polifarmacoterapia nell'addiction

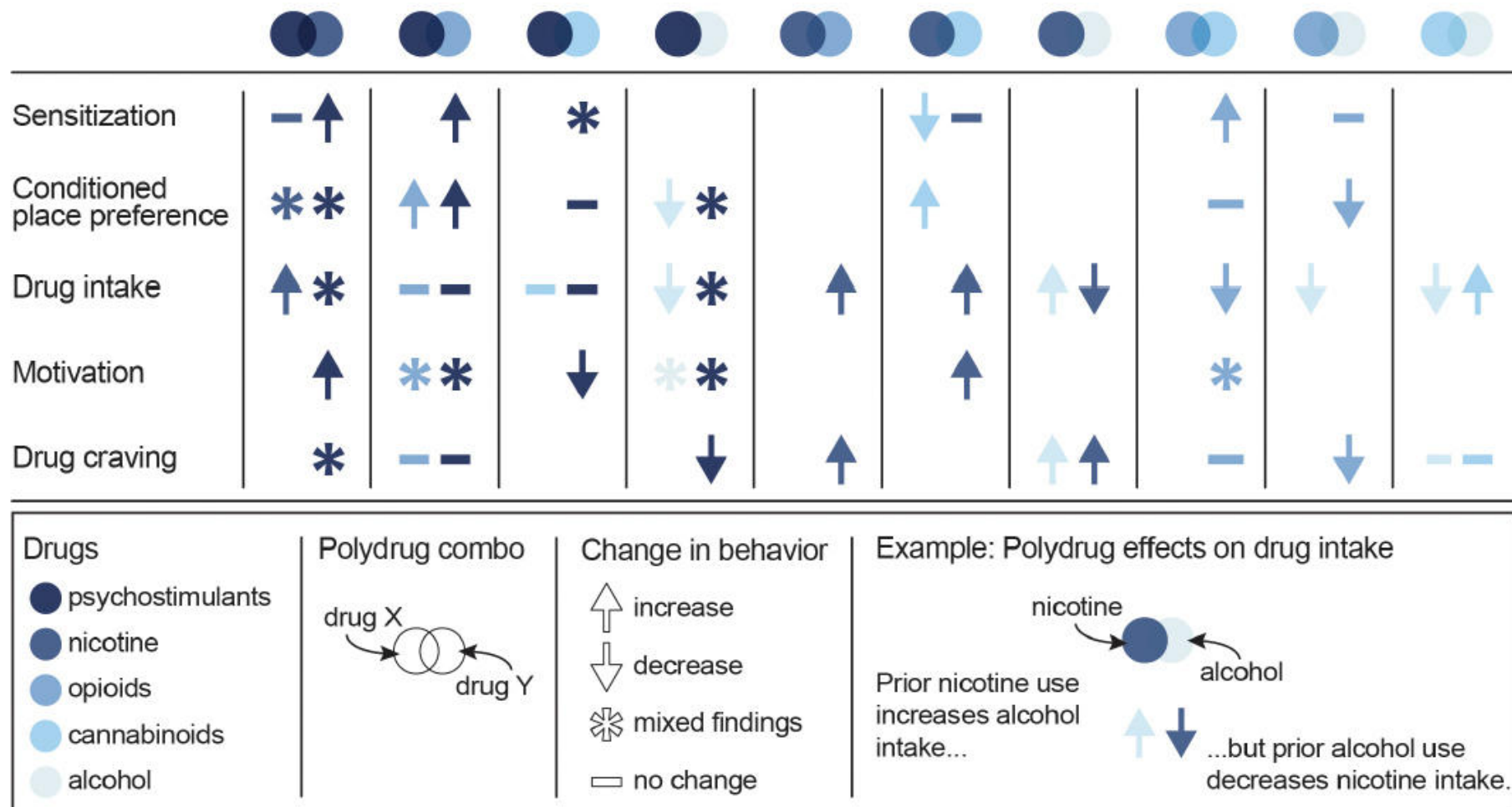
- Poliabuso
- Aggiornamento sulle interazioni farmacologiche
- Nuove formulazioni
- Gestione del rischi e monitoraggio

I Consumi

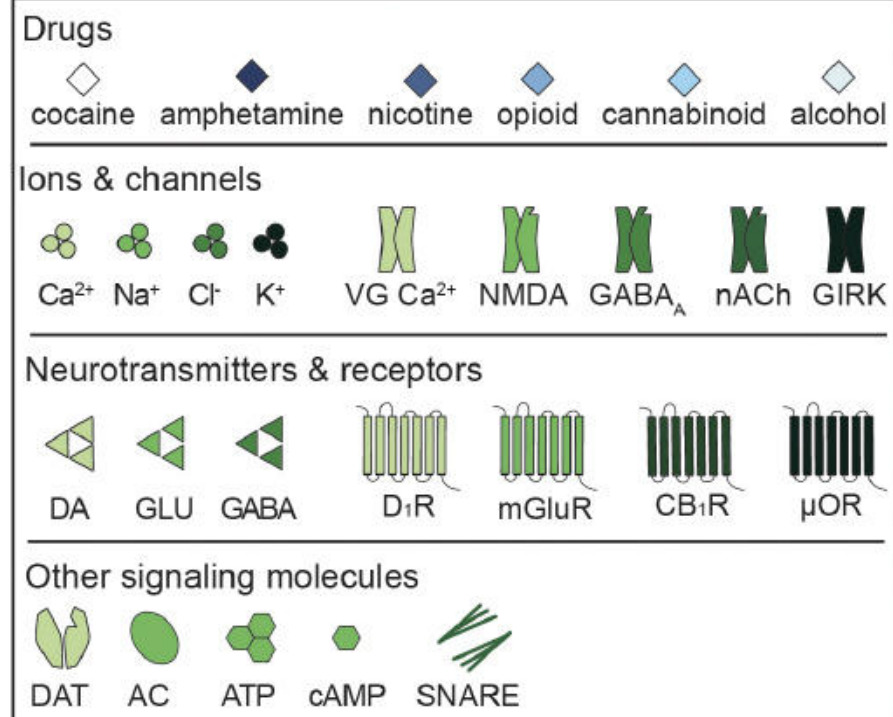
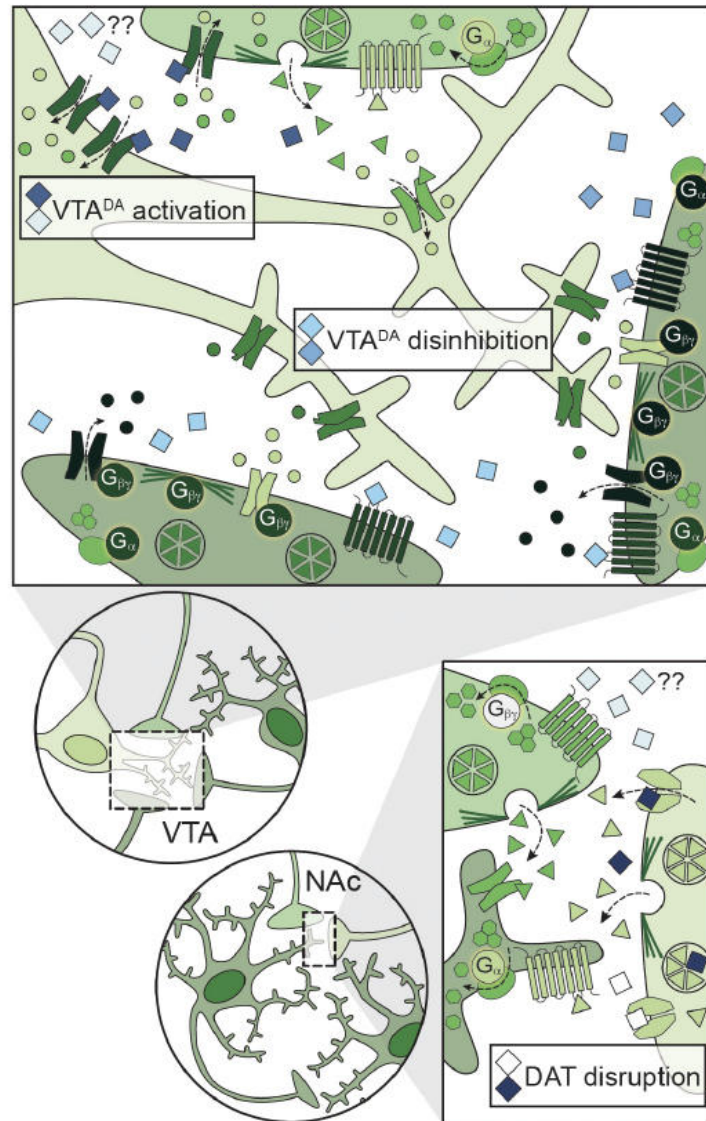
A Drug use in the United States, 1990-2019



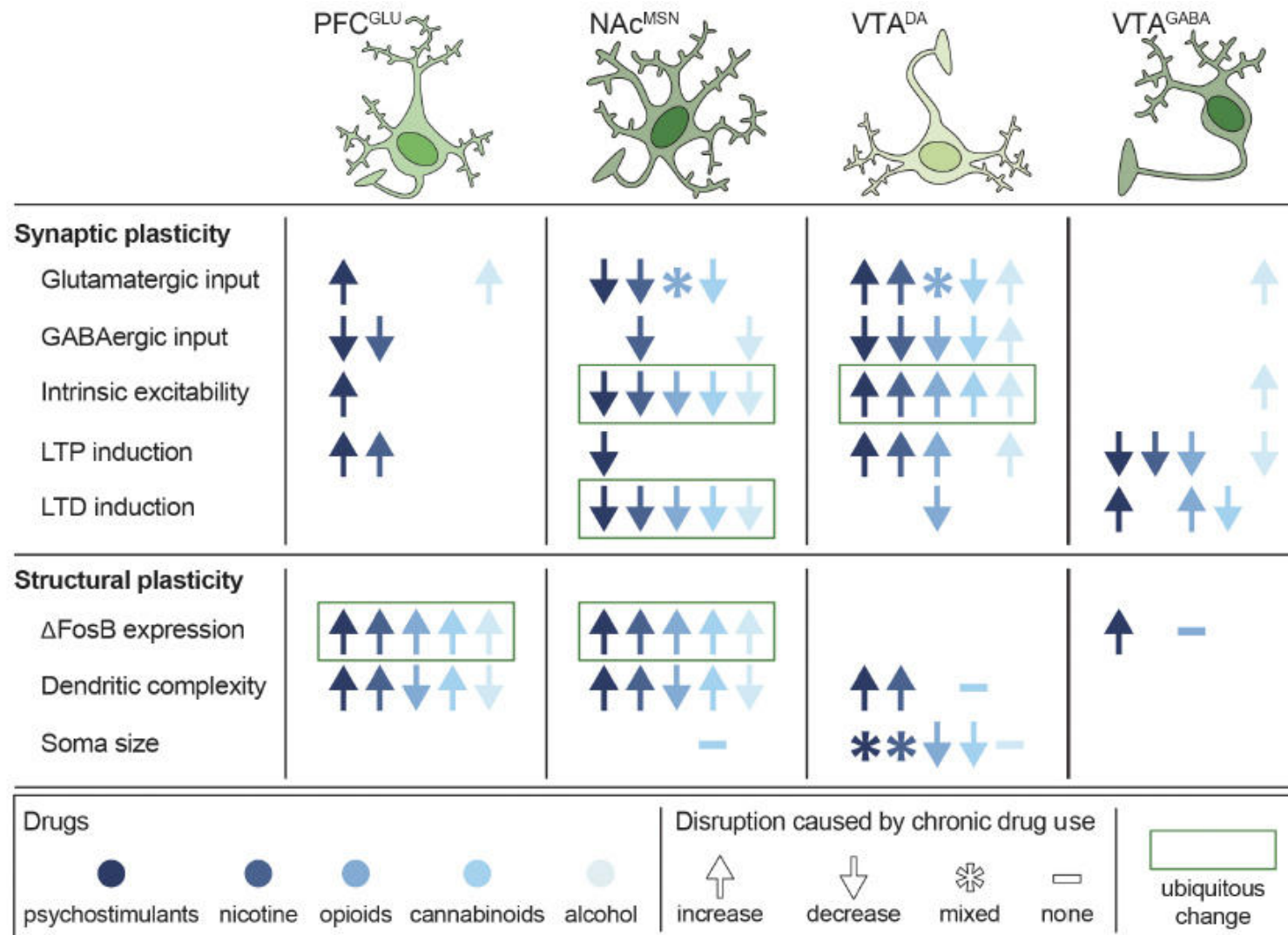
I policonsumi: implicazioni cliniche



I policonsumi: Implicazioni neurofarmacologiche (1)



I policonsumi: implicazioni neurofarmacologiche (2)



Esistono importanti interazioni farmacologiche con le principali terapie per l'addiction?

- No se...
- Le terapie vengono utilizzate secondo le indicazioni
- Le terapie sono utilizzate ai dosaggi efficaci e long term
- Non vengono associate a alcol e BDZ

Attenzione in particolare a altre categorie di sostanze d'abuso:

- Cocaina
- NSP

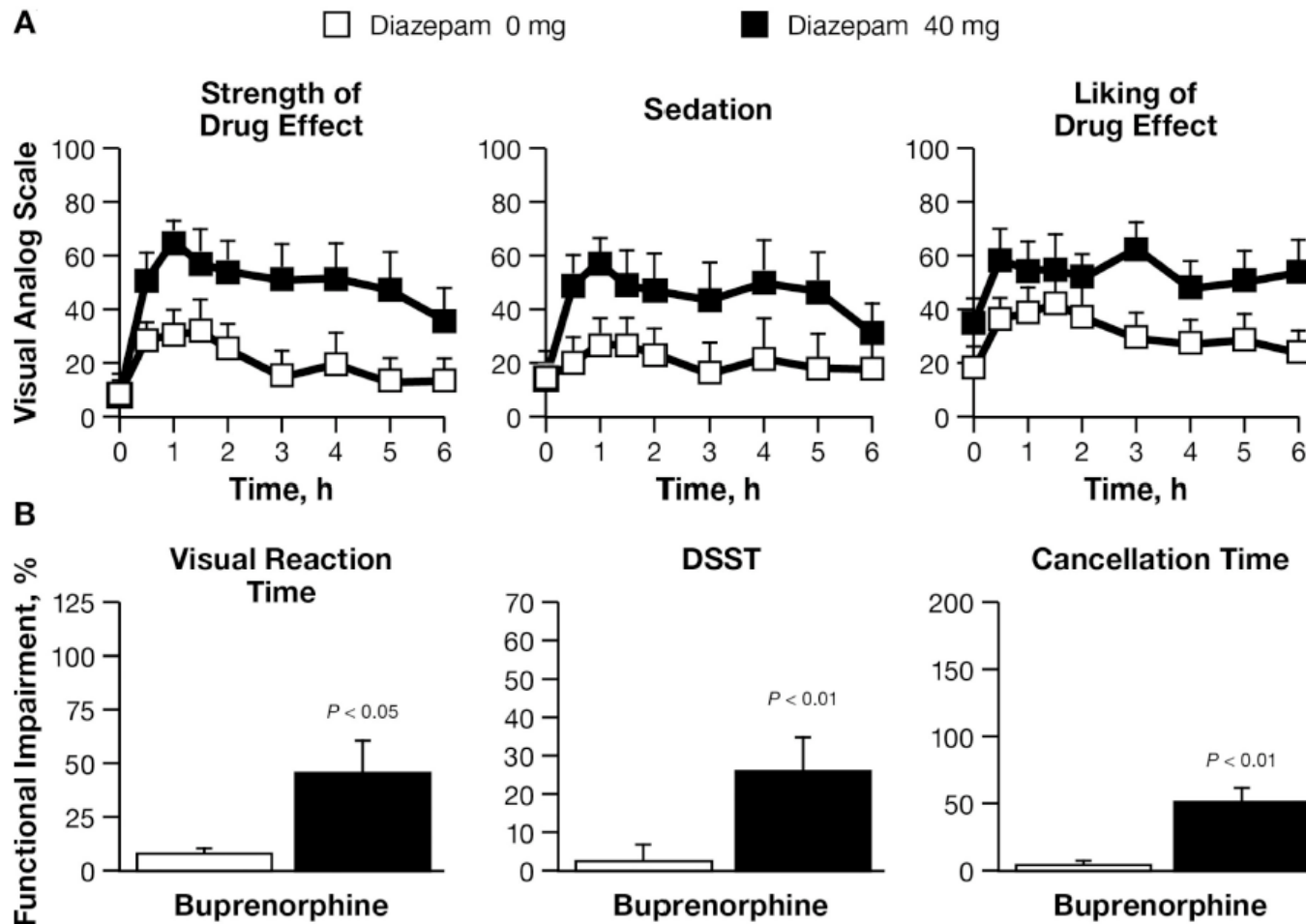
Effetti delle BDZ sulle Terapie sostitutive

Table 1

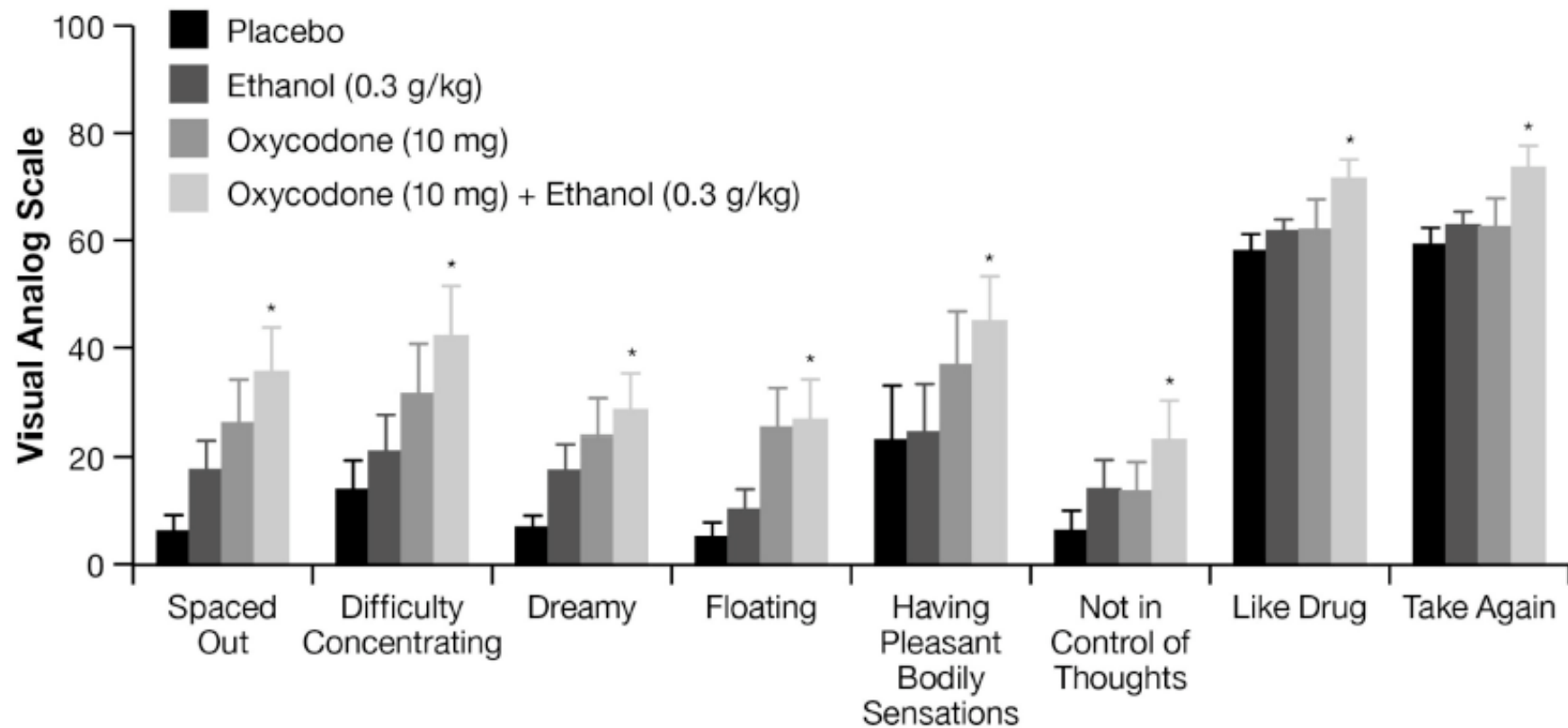
Clinical investigations of the interactions between opioids and benzodiazepines.

Author(s)	Drugs and doses	n	Outcome
Pond et al. (1982)	• Diazepam: ≈ 0.3 mg/kg for 9 days • Methadone: 50 mg $\pm$ 17	4	Diazepam failed to inhibit the metabolism of methadone
Faroqui et al. (1983)	• Diazepam: 200 μg/kg • Buprenorphine: 2 μg/kg • Buprenorphine: 3 μg/kg • Fentanyl: 1.5 μg/kg	88	Eleven patient who had received buprenorphine suffered sudden respiratory depression requiring manual ventilation of their lungs followed by doxaprain infusion
Preston et al. (1984)	• Diazepam: 20, 40 mg • Methadone: 50 or 60 mg (mean = 56 mg), 100%, 150% and 200% of normal dose	5	The pupil constriction induced by diazepam + methadone combinations was greater than that induced by comparable doses of methadone alone. Diazepam 40 mg significantly increased opioid subjective effects when compared to either drug alone
Preston et al. (1986)	• Diazepam: 20, 40 mg • Methadone: 50 or 60 mg (mean = 56 mg), 100% and 150% of normal dose	5	No evidence of a pharmacokinetic interaction between methadone and diazepam
Farre et al. (1998)	• Flunitrazepam: 1, 2, 4 mg • Triazolam: 0.5, 0.75 mg • Methadone: 40–50 mg (mean = 44 mg)	10	Flunitrazepam (4 mg) produced significantly increased ratings of "high" and "euphoria," indicating that the drug had significant abuse liability among methadone-maintenance patients
Spiga et al. (2001)	• Diazepam: 0, 5, 10, or 20 mg/70 kg • Methadone: 80 mg	5	The 10 and 20 mg diazepam doses significantly increased subjective reports of "good," "like," "strong," and "high." Pretreatment with these doses significantly decreased methadone self-administration
Lintzeris et al. (2006)	• Diazepam: 0, 10, 20 mg • Methadone: 35–100 mg (mean = 55 mg) • Buprenorphine: 6–16 mg (mean = 10.5 mg)	16	Co-administration of diazepam (10 and 20 mg) resulted in greater sedation and strength of drug effects for both methadone and buprenorphine, but had minimal impact on physiological parameters
Lintzeris et al. (2007)	• Diazepam: 0, 40 mg • Methadone: 50–100 mg (mean = 68.8 mg), 100% and 150% of normal dose • Buprenorphine: 8–16 mg (mean = 11.1 mg), 100% and 150% of normal dose	12	Diazepam 40 mg increased the intensity of subjective drug effects (strength of drug effect, sedation) and decreased psychological performance (reaction time, DSST) for both methadone and buprenorphine (independent of the opioid dose)
Zacny et al. (2012)	• Alprazolam: 0.5 mg • Oxycodone: 10 mg	20	The two drugs in combination produced stronger psychomotor effects and performance impairment. Yet, alprazolam did not alter abuse liability-related subjective effects of oxycodone

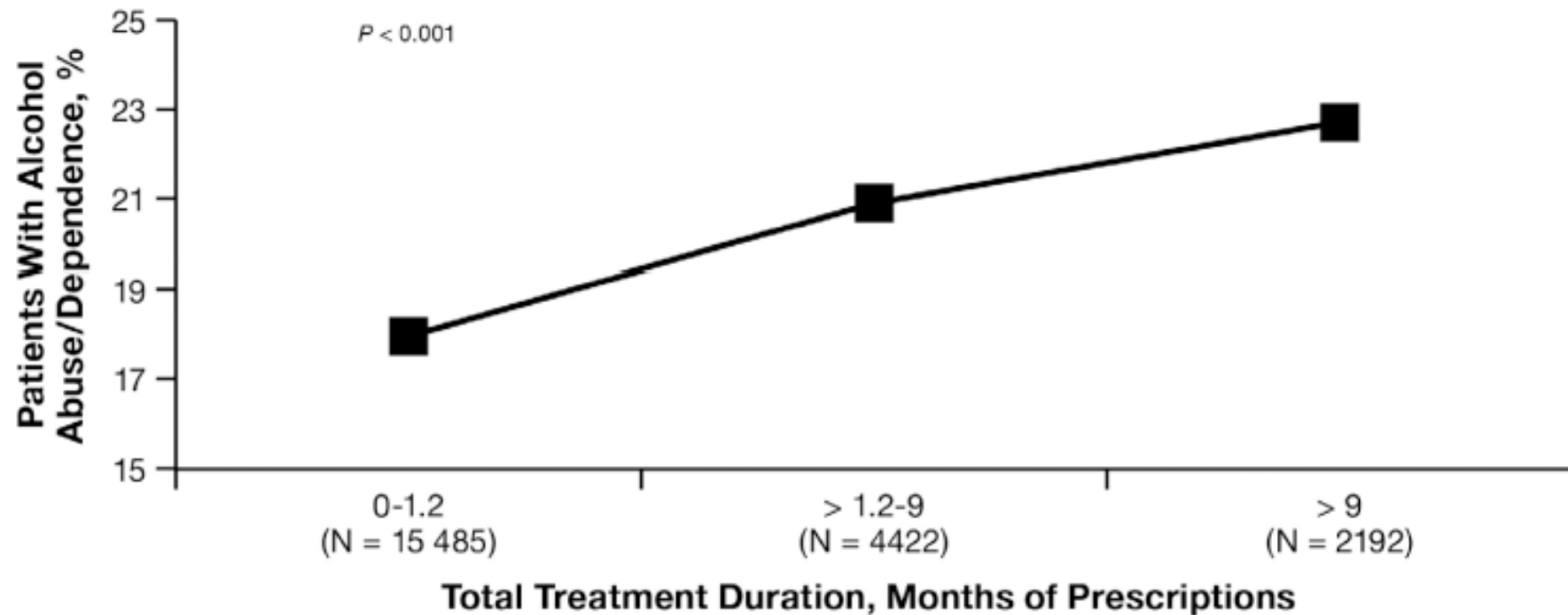
Effetti cognitivi delle BDZ in soggetti in trattamento con buprenorfina



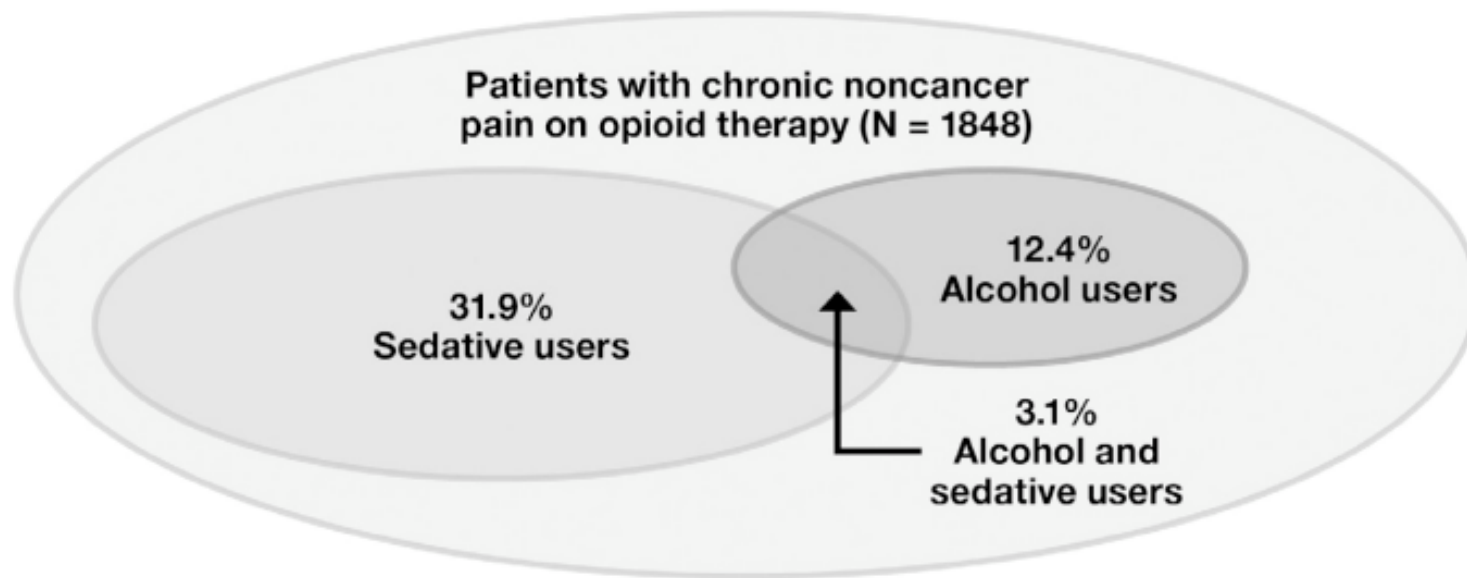
Effetti dell'ossicodone + alcol



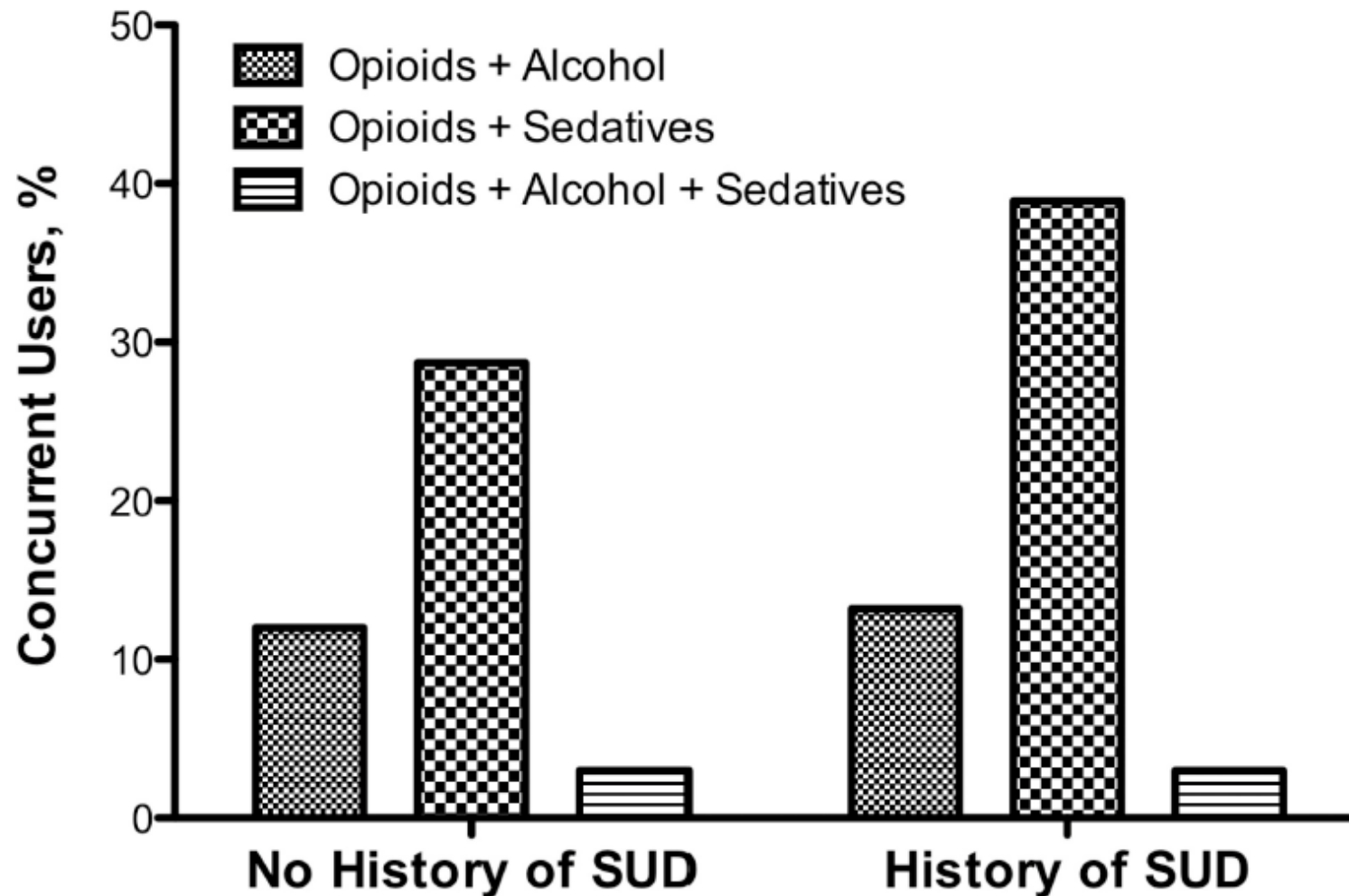
Abuso di alcol in pazienti in trattamento con analgesici oppiacei



Uso di alcol e BDZ in pazienti con dolore cronico non neoplastico e in terapia oppiacea a lungo termine



Uso di alcol e BDZ nei pz in trattamento cronico con oppiacei senza e con DUS



Effetti delle BDZ: principali interazioni

Table 1

Pharmacodynamic interactions among BDZ and different classes of medications.

Drug class	Generic name	Availability	Interaction
Opioids	Codeine Fentanyl Idromorphone Morphine Methadone Oxycodone Tramadol	Medical prescription	BDZ could enhance the effects of these drugs on the CNS, such as sedation, confusion and respiratory depression Co-administration increases the risk of addiction to these medications, through a "cross-tolerance" phenomenon
Antidepressants	Bupropione IMAO Mirtazapine Nefazodone SSRI SNRI Trazodone Tricyclic antidepressants	Medical prescription	BDZ could enhance the effects of these drugs on the CNS, such as sedation, confusion and impaired motor performances
Anticonvulsants	Carbamazepine Ethosuccimide Felbamate Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Phenytoin Phenobarbital Pregabalin Topiramate Valproic acid Vigabatrin Zonisamide	Medical prescription	BDZ could enhance the effects of these drugs on the CNS, such as sedation, confusion and impaired motor performances
Antihistamines	First-generation Antihistamines	OTC and medical prescription	BDZ could enhance the effects of these drugs on the CNS, such as sedation, confusion and impaired motor performances
Neuroleptics	Classical neuroleptics Atypical neuroleptics	Medical prescription	BDZ could enhance the effects of these drugs on the CNS, such as sedation, confusion and impaired motor performances

OTC: over the counter. Availability of medicines was analysed in the Italian pharmaceutical market.

Effetti terapie psicofarmacologiche sulle terapie agoniste

TABLE 1. Interactions between psychotropic medications and methadone or buprenorphine.

Medication	Buprenorphine	Methadone	Comments
Benzodiazepines	Caution advised	Caution advised	Risk of additive effects on respiratory depression and psychomotor impairment
Clonazepam	No effect (64)	Not studied	Human <i>in vitro</i> study
Diazepam	No effect (64)	Inhibition of methadone N-demethylation with the K_i of 50 μ M (24)	Both human <i>in vitro</i> studies
Flunitrazepam	↓FZ Metabolism by .1–2.5% (72)	↓MTD MLD	Human <i>in vitro</i> study
Midazolam	↓BPN metabolism by .08% (72) IC ₅₀ for N-BPN formation = 20.25 μ M (65)	Not studied	Human <i>in vitro</i> study
Selective serotonin reuptake inhibitors			Increased risk of QT prolongation with MTD
Paroxetine	Not studied	↓(R)-MTD metabolism by 41% and (S)-MTD metabolism by 77% (21)	Human <i>in vitro</i> study
Fluoxetine	No effect (90)	↓(R)-MTD metabolism (89)	Human <i>in vivo</i> study
Fluvoxamine	↓ BPN metabolism	↓(R)- and (S)-MTD metabolism (23)	Opioid withdrawal symptoms have been described at the sudden stop of fluvoxamine (96)
Antipsychotics			Human <i>in vivo</i> study
Quetiapine	Not studied	3–33% ↑ in (R)-MTD dose (10)	Increased risk of QT prolongation with MTD
Olanzapine	Not studied	No effect (106)	Varies with poor versus extensive metabolizers
Mood stabilizers			Human <i>in vivo</i> study
Carbamazepine	Not likely	↓MTD levels (122)	Human <i>in vivo</i> study
Valproate	No effect		Risk of MTD overdose on sudden cessation of carbamazepine
Lithium	Not studied	No effect	Human <i>in vivo</i> study
Tricyclic antidepressants			Human <i>in vivo</i> study
Amitriptyline	Not studied	↑TCA toxicity (130)	Risk of MTD overdose on sudden cessation
Desipramine	Not studied		Human <i>in vivo</i> study
Monoamine oxidase inhibitors	Contraindicated	Contraindicated	Human <i>in vivo</i> study
			Animal <i>in vivo</i> study
			Potential for serotonin syndrome

Note: MLD, minimum lethal dose; MTD, methadone; BPN, buprenorphine.

Farmaci antialcol: potenziali interazioni farmacologiche

S. Guerzoni et al

Pharmacological Research 133 (2018) 65–76

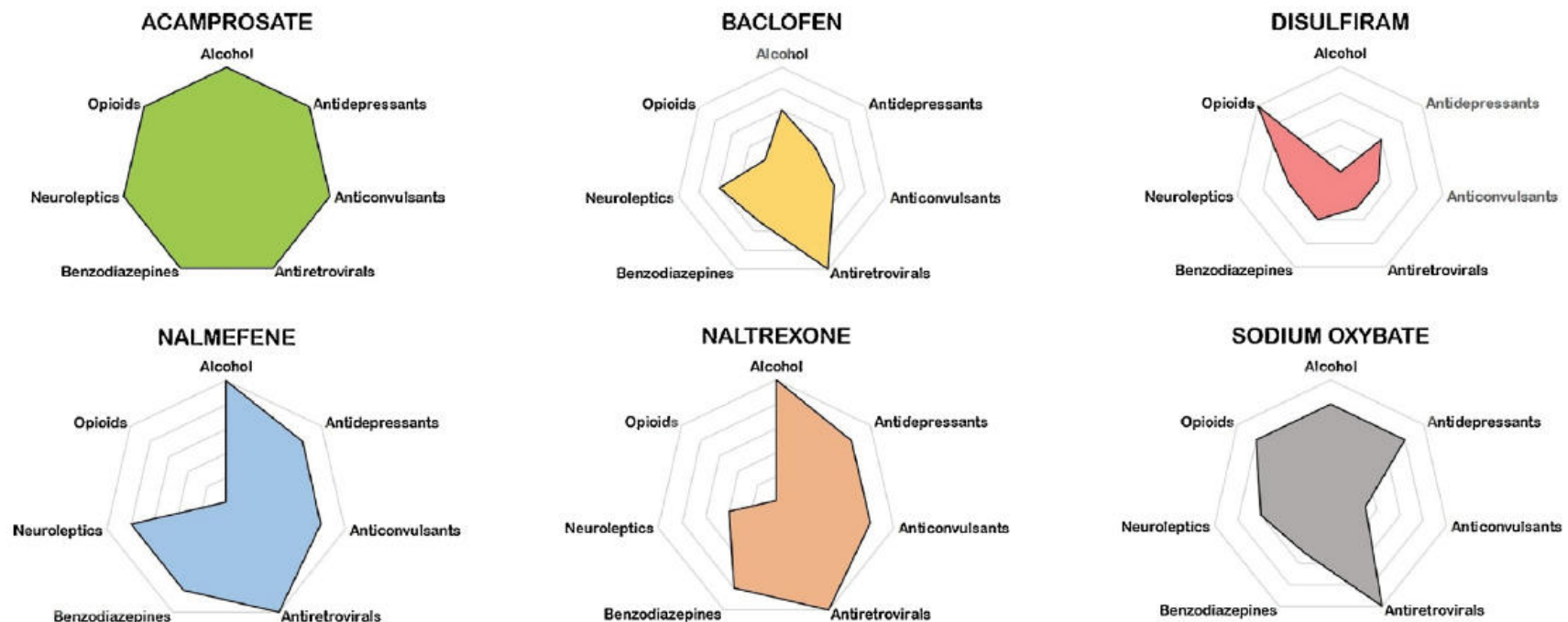


Fig. 1. Radar charts showing the potential combination of pharmacological treatments of alcohol dependence with several classes of medications. The data length of a spoke is proportional to the magnitude of the potential association between the two drugs. A line connect the data values for each spoke.

Effetti delle BDZ: interazioni farmacocinetiche

Table 2

Pharmacokinetic interactions among BDZ and different classes of medications.

Target		Drug class	Generic name	Availability
CYP3A4	Inhibitors	Azolic anti-fungal agents	Itraconazole Ketoconazole Voriconazole	OTC and Medical prescription
		Macrolids antibiotics	Erythromycin Clarithromycin	Medical prescription
		HIV protease inhibitors	Saquinavir Ritonavir Lopinavir	Medical prescription
		Calcium antagonists	Diltiazem Verapamil	Medical prescription
		Antiemetics	Aprepitant	Medical prescription
		Antidepressants	Nefazodone	Medical prescription
		Grapefruit juice		OTC
	Inducers	Anticonvulsants	Carbamazepine Phenytoin	Medical prescription
		Barbiturates	Phenobarbital	Medical prescription
		Antiretrovirals	Efavirenz Nevirapine	Medical prescription
CYP2C19	Inhibitors	Grapefruit juice		OTC
	Substrate and Inducer	Anticonvulsants	Phenytoin	Medical prescription
Glucuronidation enzymes		Anticonvulsants	Valproic acid	Medical prescription
Protein bound-drug		Digital glycosides	Digoxin	Medical prescription

OTC: over the counter. Availability of medicines was analysed in the Italian pharmaceutical market.

Disulfiram: interazioni

Table 4
Interactions between disulfiram with different classes of medications.

Pharmacodynamic interactions				
Drug class	Generic name	Availability	Interaction	
Drugs containing alcohol		Medical prescription and OTC	The association is capable of triggering the disulfiram-ethanol reaction, with serious consequences for patients	
Anticoagulants	Warfarin	Medical prescription	Disulfiram may augment warfarin hypoprothombinemia by chelating the metal cations necessary for the synthesis of active prothrombin	
Antibiotics	Isoniazid	Medical prescription	These compounds, when administered in combination, may significantly alter metabolism of brain catecholamines	
Psychostimulants	Metronidazole Amphetamine Methylphenidate Buspirone Marijuana	Medical prescription	Disulfiram interferes with the mechanism of action of these drugs, inhibiting the dopamine β-hydroxylase activity, resulting in hallucinations, behavioural disorders and/or psychosis	
Pharmacokinetic interactions				
Target		Drug class	Generic name	Availability
CYP2E1	Disulfiram inhibition	Anaesthetics	Halothane Isoflurane Sevoflurane	Medical prescription
		Methylxanthine	Theophylline	Medical prescription and OTC
		Analgesic	Paracetamol	Medical prescription and OTC
CYP3A4	Inhibitor	Antibiotics	Clarithromycin	Medical prescription
		Anti-rheumatic	Colchicine	Medical prescription
		Antiretrovirals	Atazanavir	Medical prescription
	Inducer	Antiretrovirals	Efavirenz	Medical prescription
	Disulfiram inhibition	Benzodiazepines	Chlordiazepoxide Diazepam	Medical prescription
CYP2C9	Inhibitor	Tricyclic antidepressants	Amitriptyline Desipramine Imipramine	Medical prescription
		Anticonvulsants	Phenytoin Fosphenytoin	Medical prescription

OTC: over the counter. Availability of medicines was analysed in the Italian pharmaceutical market.

Guerzoni et al., 2018, Pharmacological Res., 133: 65-76

Naltrexone e nalmefene: interazioni

Table 5

Interactions between naltrexone and nalmefene with different classes of medications.

Drug class	Generic name	Availability	Interaction
Naltrexone Opioids	Buprenorphine Codeine Fentanyl Idromorphone Morphine Methadone Nalbuphine Oxycodone Pentazocin Tramadole	Medical prescription	Co-administration decreases the effect of opioid agonists and increases the risk of a withdrawal syndrome. In rare cases, a hypersensitivity reaction to opiate agonist may occur.
Neuroleptics	Thioridazine	Medical prescription	Naltrexone enhances the effects of Thioridazine on the CNS. Two cases of excessive drowsiness and lethargy have been reported.
Alcohol disorders treatment	Acamprosate	Medical prescription	Naltrexone increases the absorption and bioavailability of acamprosate.
Nalmefene Opioids	Buprenorphine Codeine Fentanyl Idromorphone Morphine Methadone Oxycodone Tramadole	Medical prescription	Co-administration decreases the effect of opioid agonists and increases the risk of a withdrawal syndrome.

OTC: over the counter. Availability of medicines was analysed in the Italian pharmaceutical market.

Le tradizionali interazioni (1)

- Substance abuse is critical hindrance to clinical care of HIV patients.
- Drug addiction results in nonadherence to antiretroviral therapy (ART) in HIV-infected individuals.
- CYP pathways are responsible for the metabolism of all major drugs of abuse and medications, including ART.
- Induction or inhibition of CYP enzymes by either ART or drugs of abuse can cause the potential drug–drug interaction leading to adverse events.
- Decreased/abolished ART bioavailability, due to the induction of CYPs by substance abuse, may result in increased viral load and lack of response to HIV medication.
- Increased adherence to ART and novel/alternate interventions, as well as drug dose adjustments in drug users can improve the management of HIV/AIDS patients who are dependent of drugs of abuse.

Le tradizionali interazioni (2)

Table 1

Drug Interactions of Clinical Significance: Opioids and HIV Medications

Methadone		Buprenorphine	
Zidovudine	↑ zidovudine concentrations	Atazanavir/ritonavir	↑buprenorphine concentrations
Didanosine (tablets)	↓didanosine concentrations		
Stavudine	↓stavudine concentrations		
Lopinavir/ritonavir	↓ methadone concentrations		
Nevirapine	↓ methadone concentrations		
Efavirenz	↓ methadone concentrations		

Le nuove formulazioni

1. Valutare in anticipo le potenziali interazioni farmacologiche:
 - anamnesi farmacologica
 - registrazione nella documentazione clinica
 - monitoraggio
 - psicoeducazione

Fattori predittivi

Table 1
Predictors of Concurrent Alcohol and/or Sedative Use in Patients on Long-term Opioid Therapy for Pain^{27,52}

Predictors of Concurrent Alcohol Use	Predictors of Concurrent Sedative Use
• Male ($P = 0.0001$) • Taking opioids at doses < 120 mg morphine equivalents ($P = 0.006$) • Lower average pain intensity ratings ($P = 0.045$) • Alcohol use disorder^a ($P = 0.0003$) • Risky drinking behavior^a ($P < 0.0001$)	• Female ($P = 0.0001$) • Younger age ($P = 0.0006$) • Depression ($P < 0.0001$) • Anxiety or sleeping problem ($P \leq 0.011$) • Using opioid for > 1 pain condition ($P = 0.0005$) • Taking opioids at high doses^b ($P < 0.0001$) • Any substance use disorder identification ($P = 0.002$)

^a Alcohol use disorder and risky drinking behavior were defined by the Alcohol Use Disorders Identification Test–Consumption.

^b High opioid doses were defined as daily doses ≥ 120 mg.

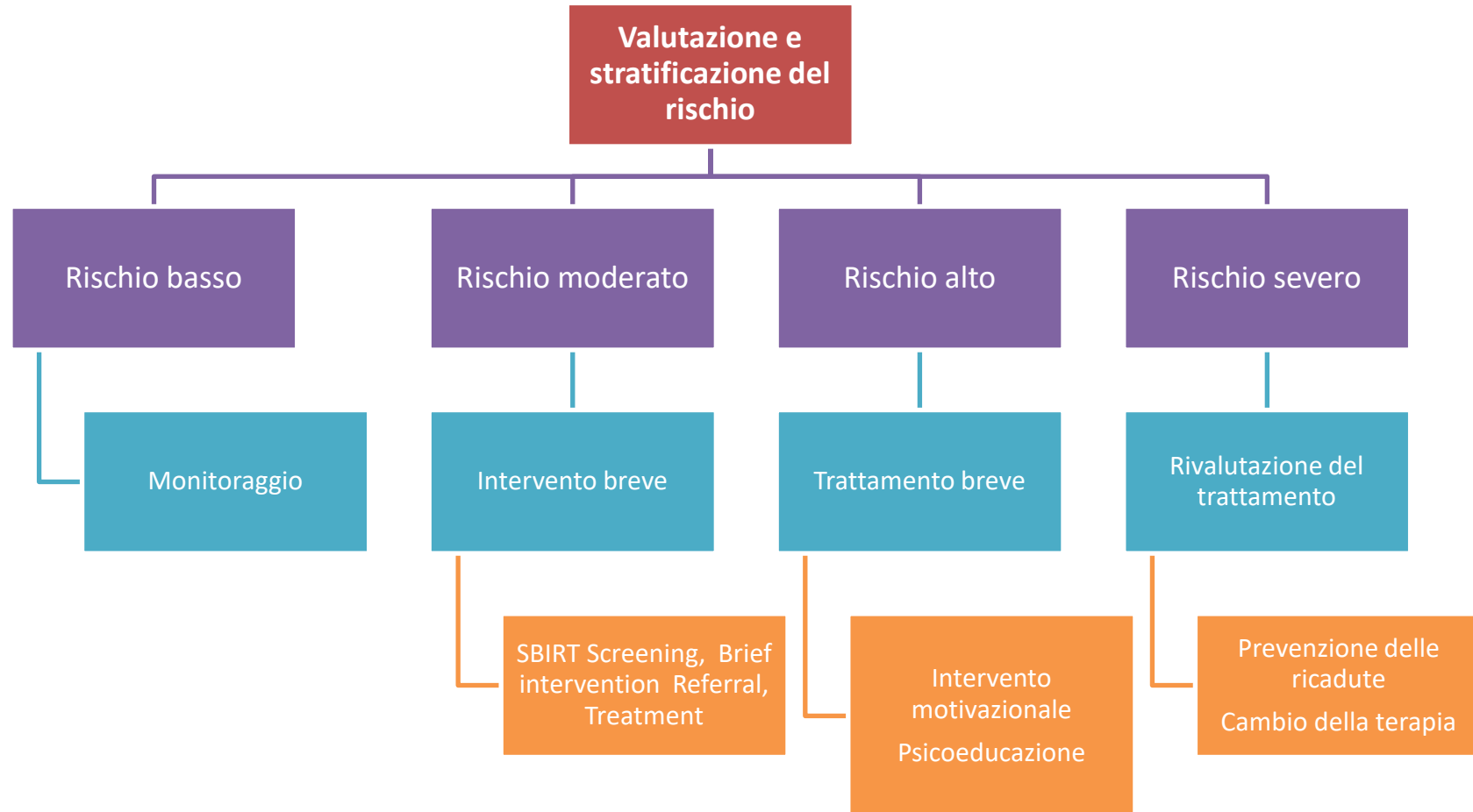
Il Management clinico delle interazioni farmacologiche

- La valutazione del rischio in termini di comorbidità e mortalità:
 - valutazione multidimensionale dal punto di vista dei comportamenti di consume, psichiatrico e delle comorbidità mediche
- Monitoraggio dell'aderenza al trattamento
 - non soltanto dei trattamenti per le dipendenze
- Screening tossicologico delle urine
- Valutazione e stratificazione del rischio e azioni di mitigazione

Il Management clinico delle interazioni farmacologiche

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Valutazione e stratificazione del rischio



Risk management

Ogni effetto di una interazione farmacologica deve essere considerato:

- un evento sentinella:
 - segnalato (risk management)
 - gestito (audit)
 - corretto

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