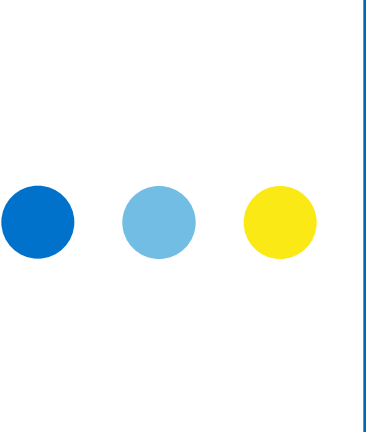
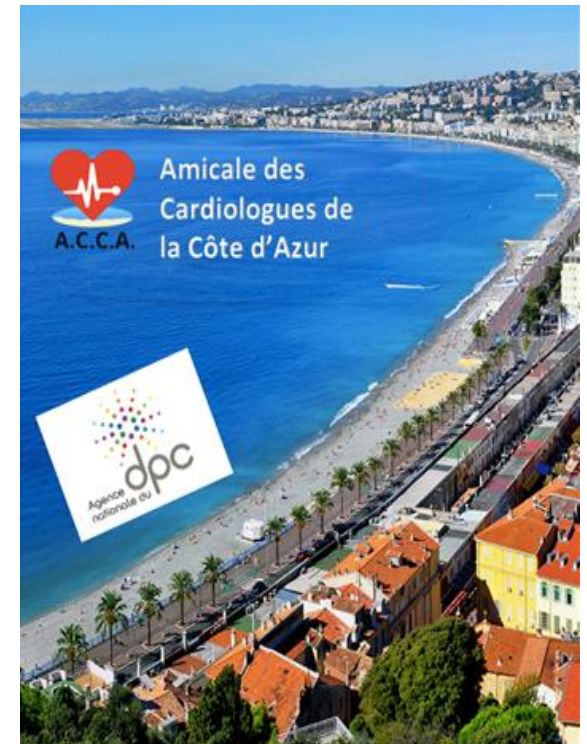




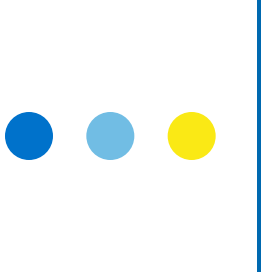
Cœur et Substances Récréatives

Milou-Daniel DRICI, FESC
Pharmacovigilance
Université de Nice Côte d'Azur



JOURNÉE D'ACTUALITÉS THÉRAPEUTIQUES

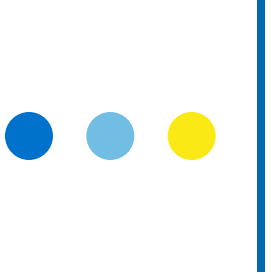
Samedi 14 Avril 2018



Disposal for Prescription and Recreational Drugs

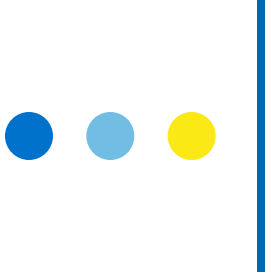
Pursuant to Clark County Code 20.04.090, it is unlawful to possess or advertise marijuana/cannabis/THC on Clark County Department of Aviation-owned property.

Penalties include but are not limited to prosecution, arrest, civil and/or criminal fines, or a combination thereof.



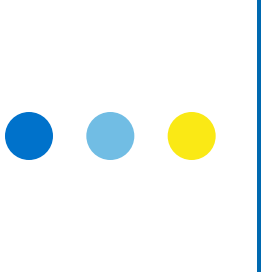
Déclaration d'intérêt

- ANSM :
 - Gpe de travail cardio
 - CT pharmacovigilance
- EMA :
 - SAG Cardio
- DSMB (aucun financement personnel)
 - SANOFI



Sujet jeune

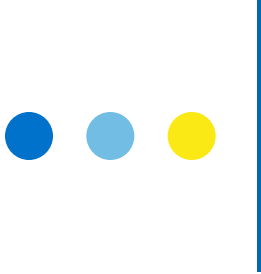
- Cannabinoïdes de synthèse,
- boissons dites « énergisantes »
- autres causes exogènes d'ischémie cardiaque chez le jeune
- « Poppers »



Abus de substances « récréatives »

- Drogues psychoactives répandues ++
 - plantes, médicaments, drogues,
 - « new psychoactive substances » (NPS)
 - Internet connaissance (Forums...) et accessibilité
- Enfants et adolescents:
 - Marijuana > Inhalants > NPS
 - cannabinoïdes et les cathinones

Johnston LD et al. National survey on drug use 1975-2012, Castellans D et al. 2016.
Halpern et al, 2001 , Schifano et al, 2006, Davey et al, 2012



Ischémie myocardiques au cours de ces intoxications volontaires

↑PAS, PAD et FC

↑débit cardiaque et la consommation d' O²

↑ Catécholamines (↓ reuptake)

- Sensibilisation cardiaque aux catécholamines

Récepteurs spécifiques (CB1, CB2...)

- Troubles du rythme → Mort Subite
- Douleurs angineuses → SCA, IDM

● ● ● | La concentration en Δ^9 -THC a été multipliée par 3 ces 15 dernières années....



<http://ansm.sante.fr/s-informer>

Evolution of THC content over the years

- < 2% in 1980
- 4.5% in 1997
- 8.5% in 2006 (El Sohly et al., 2000)
- 8.8% in 2008 (Mehmedic et al. 2010)
- > 20% in 2015, some in the USA !

In Europe it concerns 8.8 M people 15 to 24 y.o.



The health and social effects of nonmedical cannabis use. World Health Organization 2016

Cannabis in adults

- Acute exposure ↑HR, BP
- acute coronary syndromes ++
 - Marijuana associated with 4~5 fold more MI <1 hr
 - In stable CAD : ACS occur faster than with tobacco
 - Cannabis-related CV complications ~2%
 - 25% mortality (addictovigilance reports)
- In children and adolescents ?

Rezkalla S et al. 2014; J Am Heart Assoc; Pacher & Kunos, 2013; Schmid et al., 2010, Jouanous, 2014, Mittleman et al 2001 Montecucco & Di Marzo, 2012
Gottschalk, Aronow & Prakash, 1977, Aronow & Cassidy, 1974

CASE REPORT

Coronary Vasospasm in an Adolescent Resulting from Marijuana Use

Sangita Basnet · Gurpreet Mander ·
Ramzi Nicolas

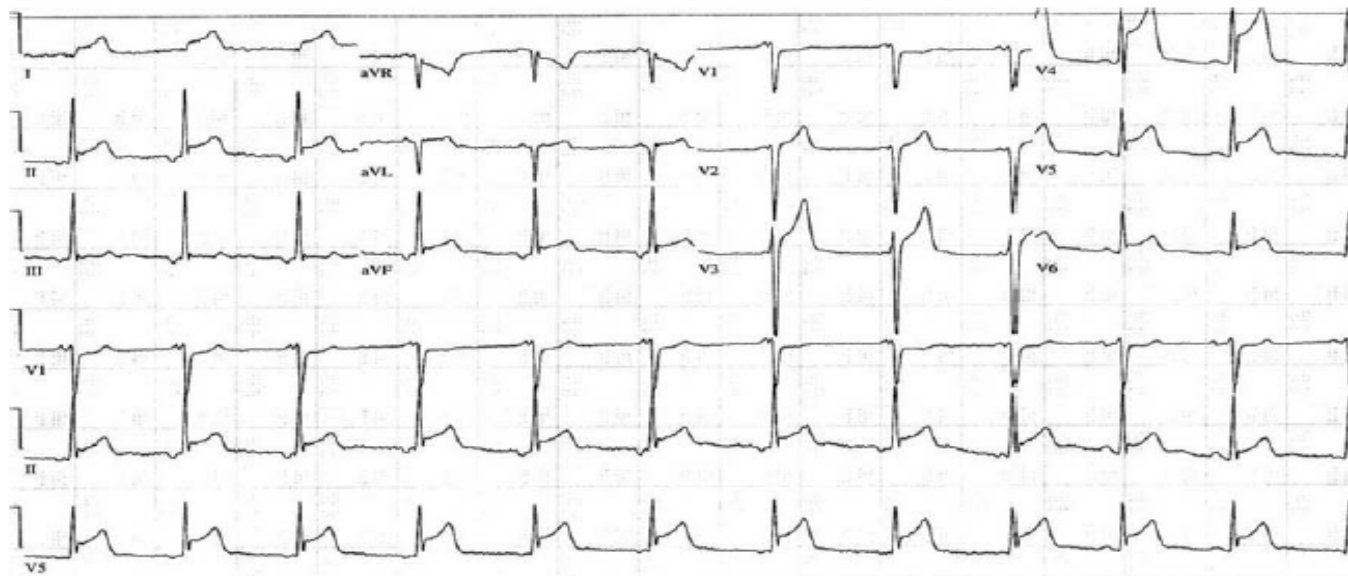


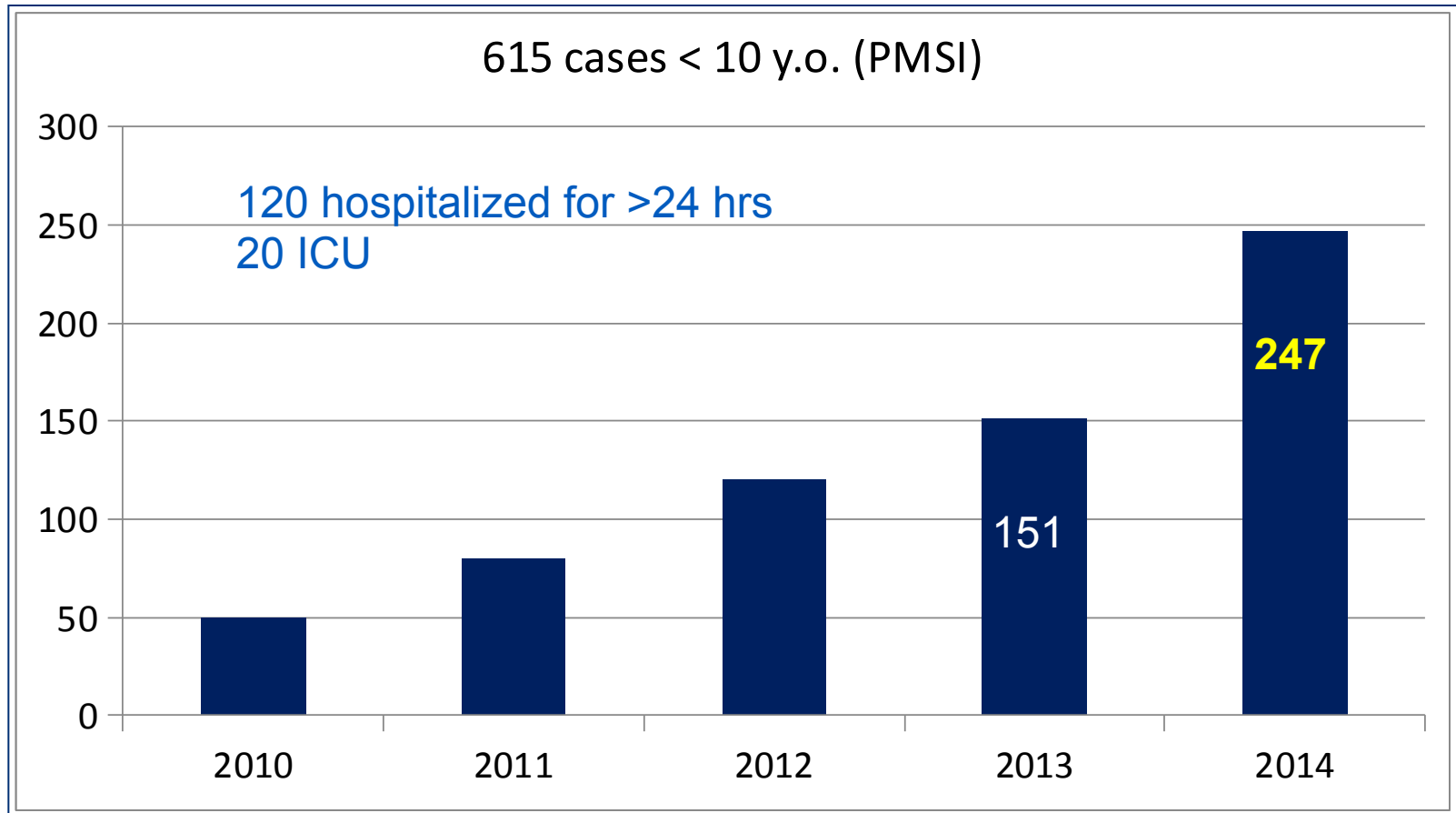
Fig. 1 Electrocardiogram (ECG) showing ST segment elevation in lateral leads



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Sophia Antipolis

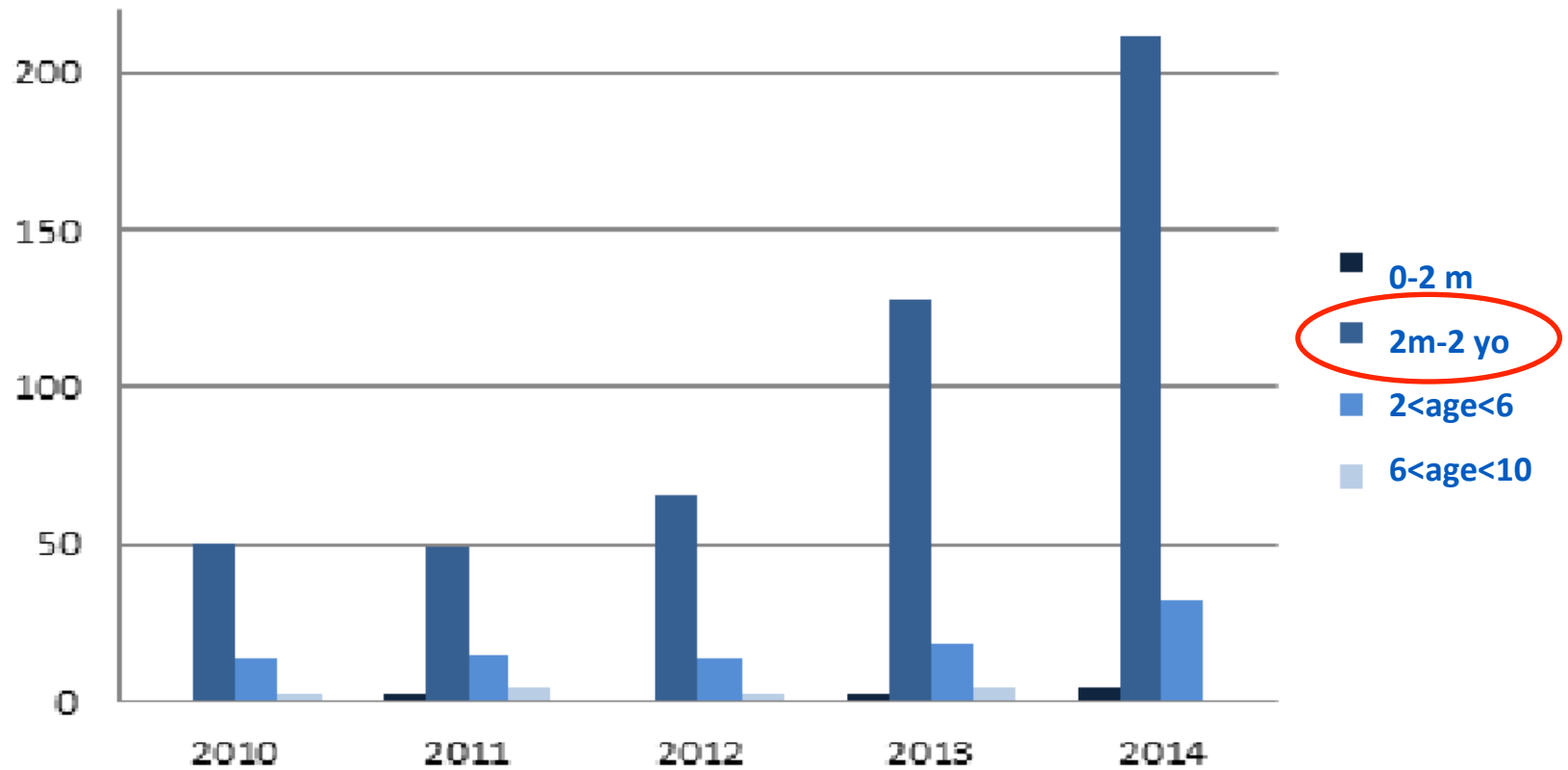
CRPV
Nice Alpes Côte d'Azur

Intoxications pédiatriques au cannabis en France



Intoxications notifiées aux CEIP (France)

Age Profile



Tendance similaire Espagne, IT, USA, Maroc, Israël

Drici. ACCA 14 04 2018



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Inhalants



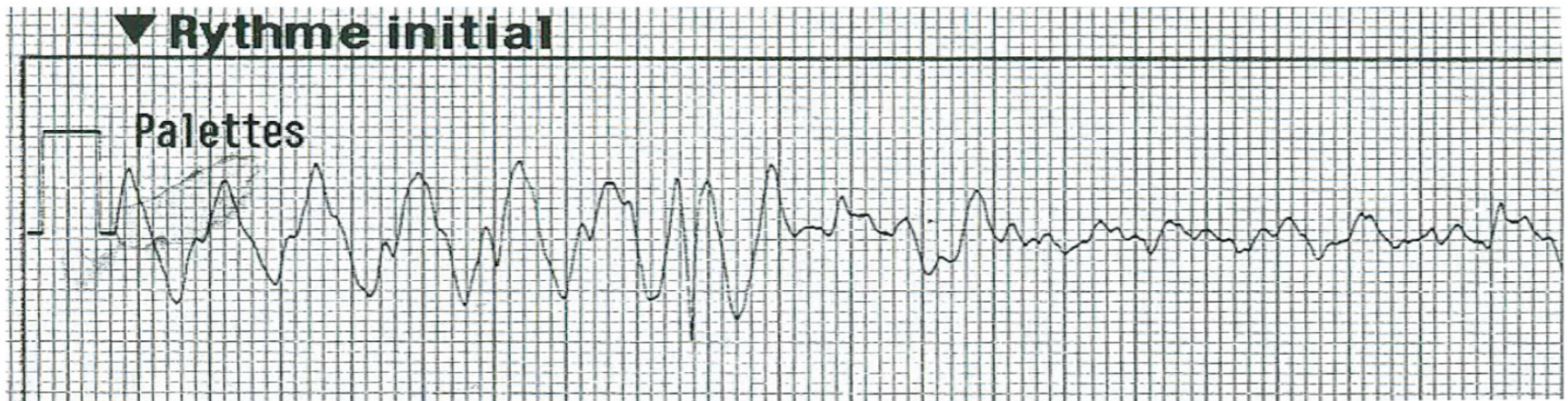
- Hundreds legally available volatile substances inhaled intentionally to “get high” (including propellants)
 - Huffing, bagging, sniffing, dusting...
- 1987 ⇕ CFC, replaced by butane or propane
- Rapid C_{max} , cardiac ischemia (solvents ++)
 - Irreversible coronary spasm
 - cardiac sensitization to catecholamines
 - proarrhythmic (continuous ECG monitoring)

Sudden sniffing death

- Gillet B et al, 2014 Tox Anal Clin; 26: 110-154

15 y.o., deodorant propellant (isobutane)

5% of death in this class of age



- white male children ~10 yo to ~ puberty
- last for a short period of time
- Hidden intoxication, no witness 'normal family life'



Volatile Solvents

Adhesives	model airplane glue, rubber cement, household glue
Aerosols	spray paint, hairspray, air freshener, deodorant, fabric protector, computer keyboard cleaner
Solvents and gases	nail polish remover, paint thinner, type correction fluid and thinner, toxic markers, pure toluene, cigar lighter fluid, gasoline, carburetor cleaner, octane booster
Cleaning agents	dry cleaning fluid, spot remover, degreaser
Food products	vegetable cooking spray, dessert topping spray (whipped cream), whippets
Gases	nitrous oxide, butane, propane, helium



New Psychoactive Substances

- unregulated mind-altering drugs newly available on the market
 - intended to mimic effects of (il)legal drugs
 - France (2015) : 43 substances
 - Europe (since 1997) : 450
 - 2/3 synthetic cannabinoids and cathinones
- US ~ 1.2 M users
 - 10,607 cases lead to ER (2009)

New Psychoactive Substances

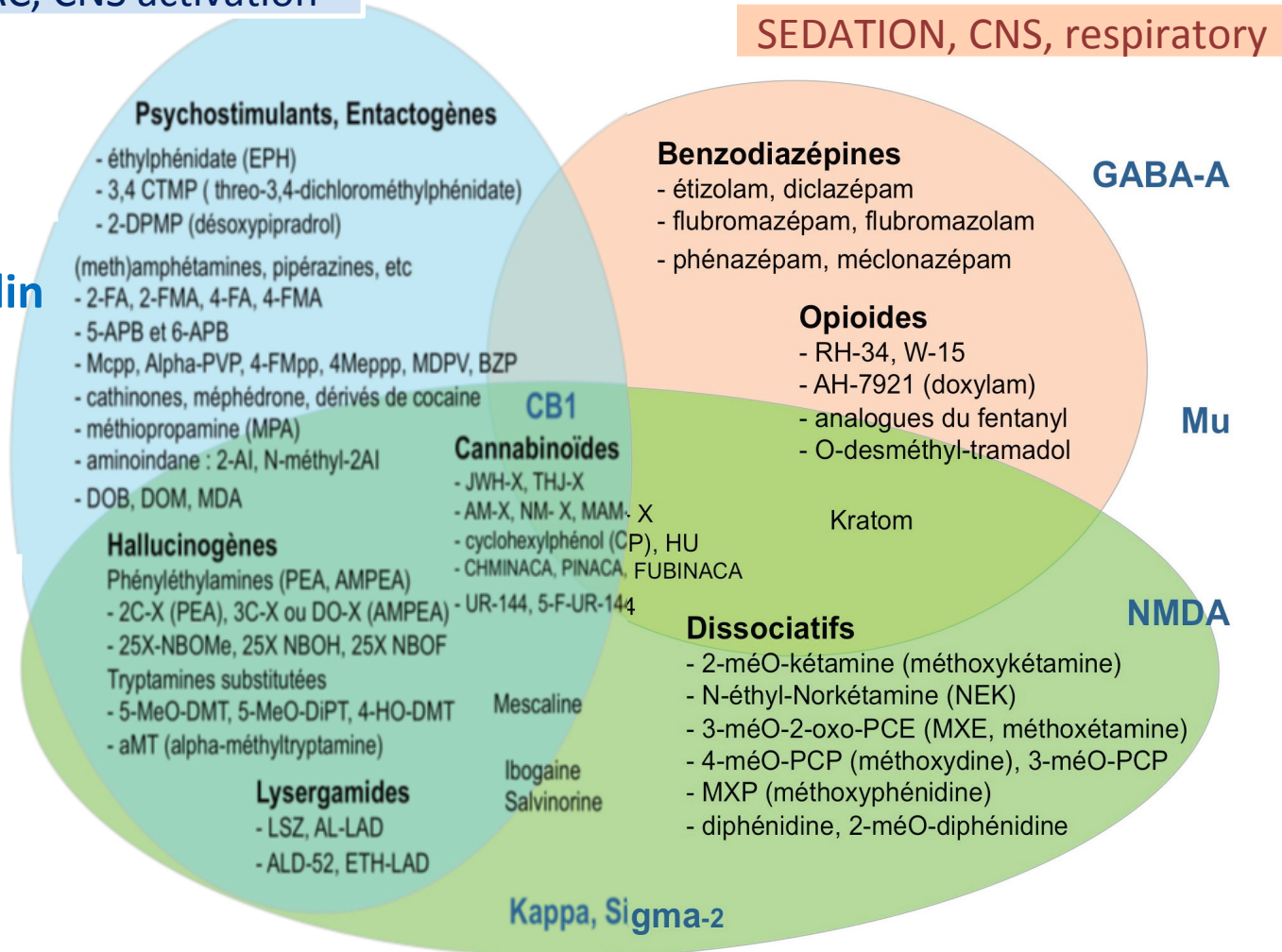
Research Chemicals, Designer Drugs, « Legal Highs »

CARDIAC, CNS activation

SEDATION, CNS, respiratory

Dopamine
Noradrenalin
Adrenalin
Serotonin

Serotonin



New Psychoactive Substances

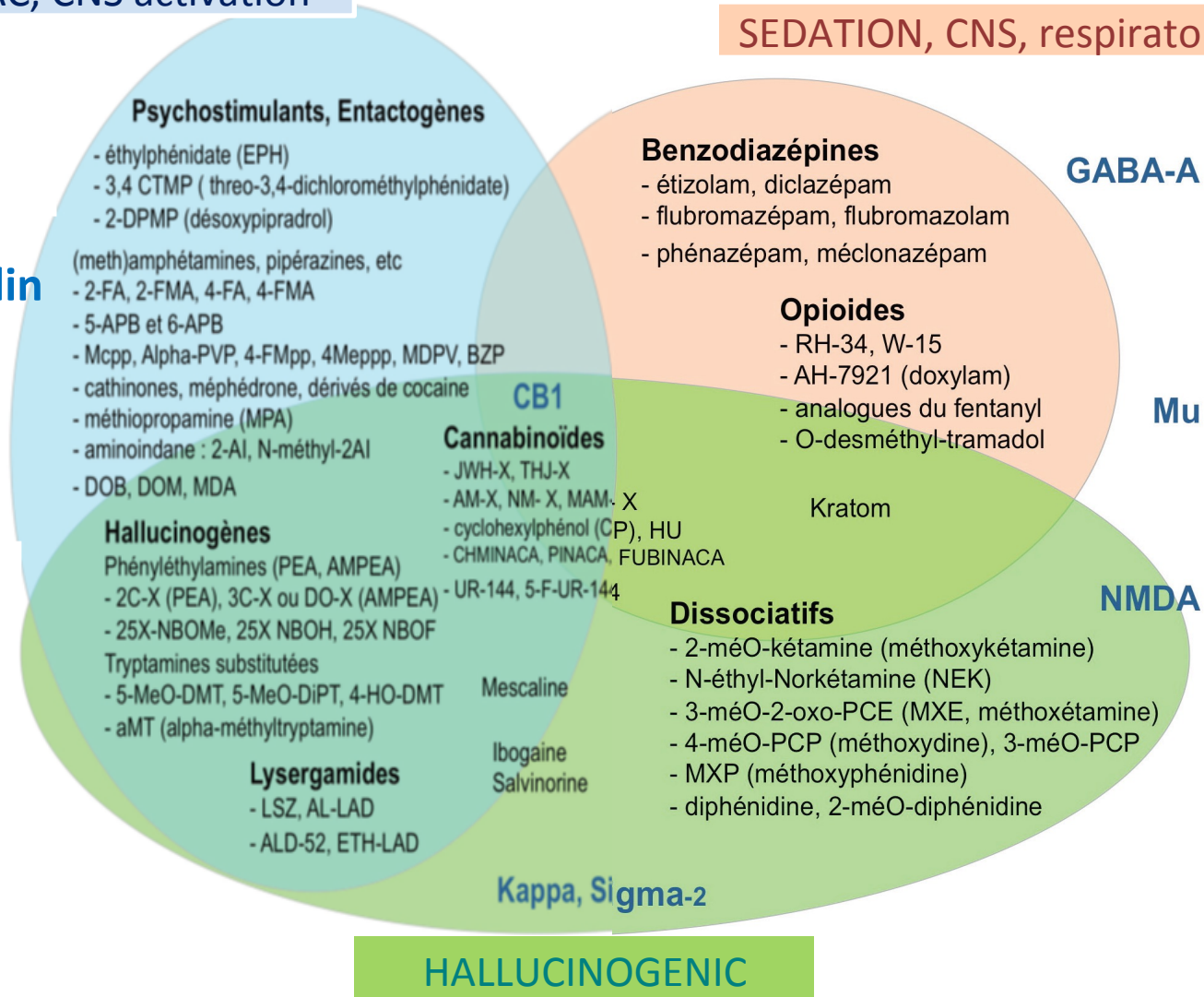
Research Chemicals, Designer Drugs, « Legal Highs »

CARDIAC, CNS activation

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Dopamine
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Serotonin



CENTRE HOSPITALIER UNIVERSITAIRE DE NICE - HOPITAL PASTEUR
LABORATOIRE DE PHARMACOLOGIE-TOXICOLOGIE

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ue de la Voie Romaine - CS511069 - 06001 Nice cedex 1

Tél : 04.92.03.85.02 Fax : 04.92.03.77.91 E-mail : pharmacologie@unice.fr

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NEUROVASCULAIRE HC
HOPITAL PASTEUR 2

PISTAGE TOXICOLOGIQUE URINAIRE

Barbituriques

Non détectés

Benzodiazépines

Non détectées
L'interprétation du résultat doit tenir compte du contexte clinique.

Amphétamines

Non détectées

Cannabinoïdes

Non détectés

Cette technique ne permet pas la détection des cannabinoïdes de synthèse (Spice, K2...).

Non détectés

Non détectés

antérieur :

antérieur :

antérieur :

antérieur :

antérieur

antérieur

antérieur

Synthetic cannabinoids “K2” or “Spice”

Man-made chemicals sprayed on dried plant material to be smoked, (or E-cigarette liquid, ‘liquid incense’) :
Joker, Black Mamba, Krush, Kronik...

- widespread
- undetectable
- similar to delta-9 *THC*
 - greater affinity for CB1 and CB2
 - serotonin
- **↑ Blood pressure and tachycardia**
- **↓ Blood supply to the heart**



Source: National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services. Synthetic cannabinoids. 2015:1-3; Kemp AM et al. Am J Med. 2016;129(3):240-44

Cardiac ischemia with 'K2'

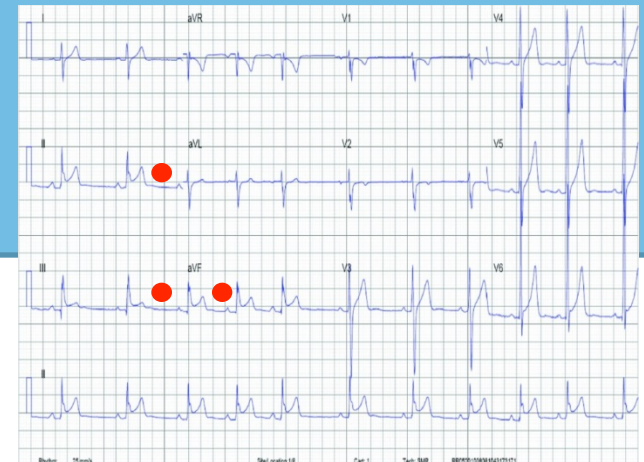
16 yo, retrosternal pain 24 hours, TNT resistant, Troponin peaked at 33 ng/ml. Normal echo, angiogram normal on the 4th day

McKeever RG et al. 2015. J Med Toxicol 11:129-31



16 yo high school athlete, retrosternal pain for 3 days , Troponin peaked at 25 ng/ml. Normal echo, angiogram normal

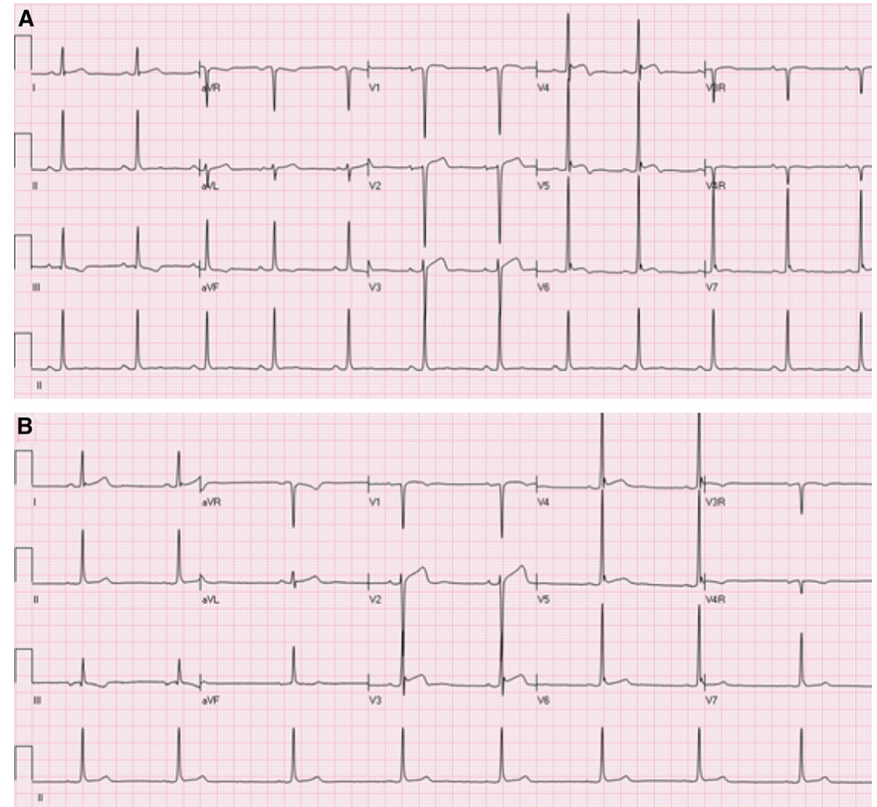
Vir A. et al. 2011. Pediatrics (128) : 1622-27



Undetectable by routine urine testing...

Patients characteristics with *K2*

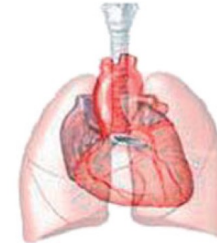
- All males, 16 ± 1 yo
- Chest pain
- ECG :
 - ST elev. 6/8
 - ST abnorm. 2/8
- Echo : Normal 6/6
- Troponine:
 - normal 4/7
 - elevated 2/7



Clark BC et al. J Pediatr 2015;167:757-61).

Role of CB1 and CB2, CBe ?

- vasospasm from increased discharge ++
- VSMC and endothelium
 - experimental vasodilation
- Hemodynamic stresses & and plaque rupture
 - MMP-9 release from lipid rich plaques
 - thrombosis formation ?



Lung CB1,CB2

Cardiovascular system CB1,CB2

Stanley C et al. Brit. J. Pharmacol. 171,1361-78 (2014)

Singla S et al. Clin. Cardiol. 35, 6, 329–335 (2012)

NPS : Amphetamines (Phenylethylamines)

- High 5-HT affinity (5-HT1B and 5-HT2A)
- 'Ecstasy' : MDMA
 - 3,4-methylene dioxyamphetamine (MDA)
 - proliferative disease thickening of cardiac valves,
 - Acute coronary constriction
- Methoxy-substituted
- on buffers NBOMe « Smiles », « Nbomb »...



Suzuki J et al. Psychosomatics. 2015;56(2):129-39

Lawn W et al. J Psychopharmacol. 2014;28(8):780-8.

Kaumann A &, Levy F. Pharmacology & Therapeutics 2006 (111): 674–706

NPS : Synthetic Cathinones

‘bath salts, legal highs, plant foods’

- synthetic phenylalkylamines mimicking Khat (*Catha edulis*) insufflated (key) or ingested (bombing)
 - Mephedrone, methylone...
 - Head shops, Internet, mixed in ‘Ecstasy’ pills
- amphetamine-like sympathomimetics
 - 51% clubgoers have had them in UK !



So called 'Energy drinks'

- 8 yo male child (26 Kg)
3 cans of Red Bull®
- ER for precordial pain 45 min.
- 160/72 mmHg HR :115 bpm
 - Normal ECG
 - Normal echo
 - Normal cardiac enzymes

Caffeine, glucuronolactone, taurine

- 1,7-dimethylxanthine
- 3,7-dimethylxanthine (theobromine)
- 1,3-dimethylxanthine (theophylline)

Caffeine syndrome

- Palpitations, headache, nervousness, hot flushes
- Elevated BP, tachycardia

Miners & Burkett 1996, Heckman et al 2010, ANSES 2013

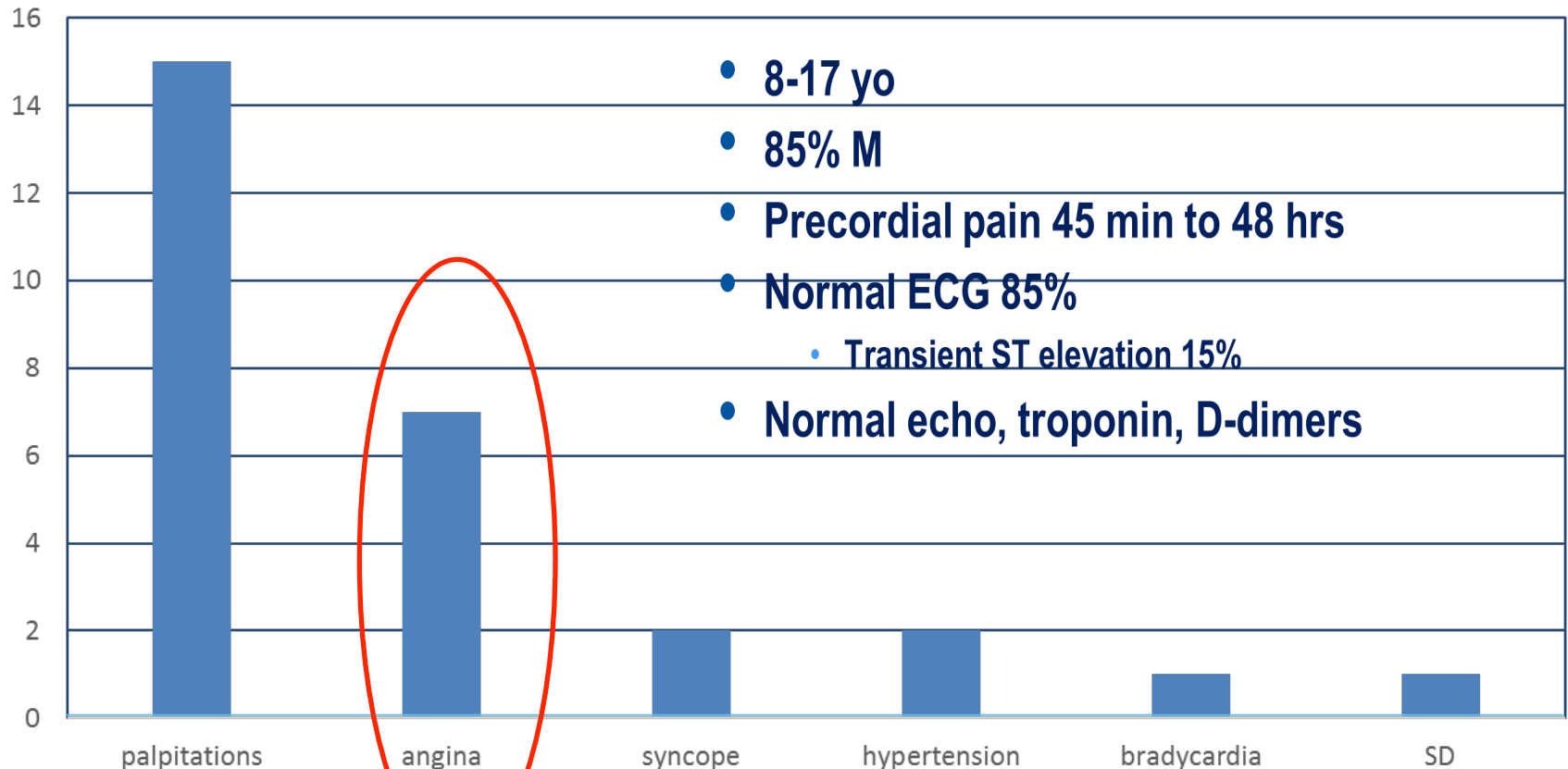


“Energy drinks” in children

- USA(2007)
 - >2500 caffeine ODs in children and adolescents
- Europe :
 - From 18% (3-10 yo) to 68% (10-18 yo) drank at least one ‘ED’ the previous year
 - >10% being regular or significant users
- France > 30 Millions liters per year
 - 1/3rd supermarkets, Red Bull® ~ 52%

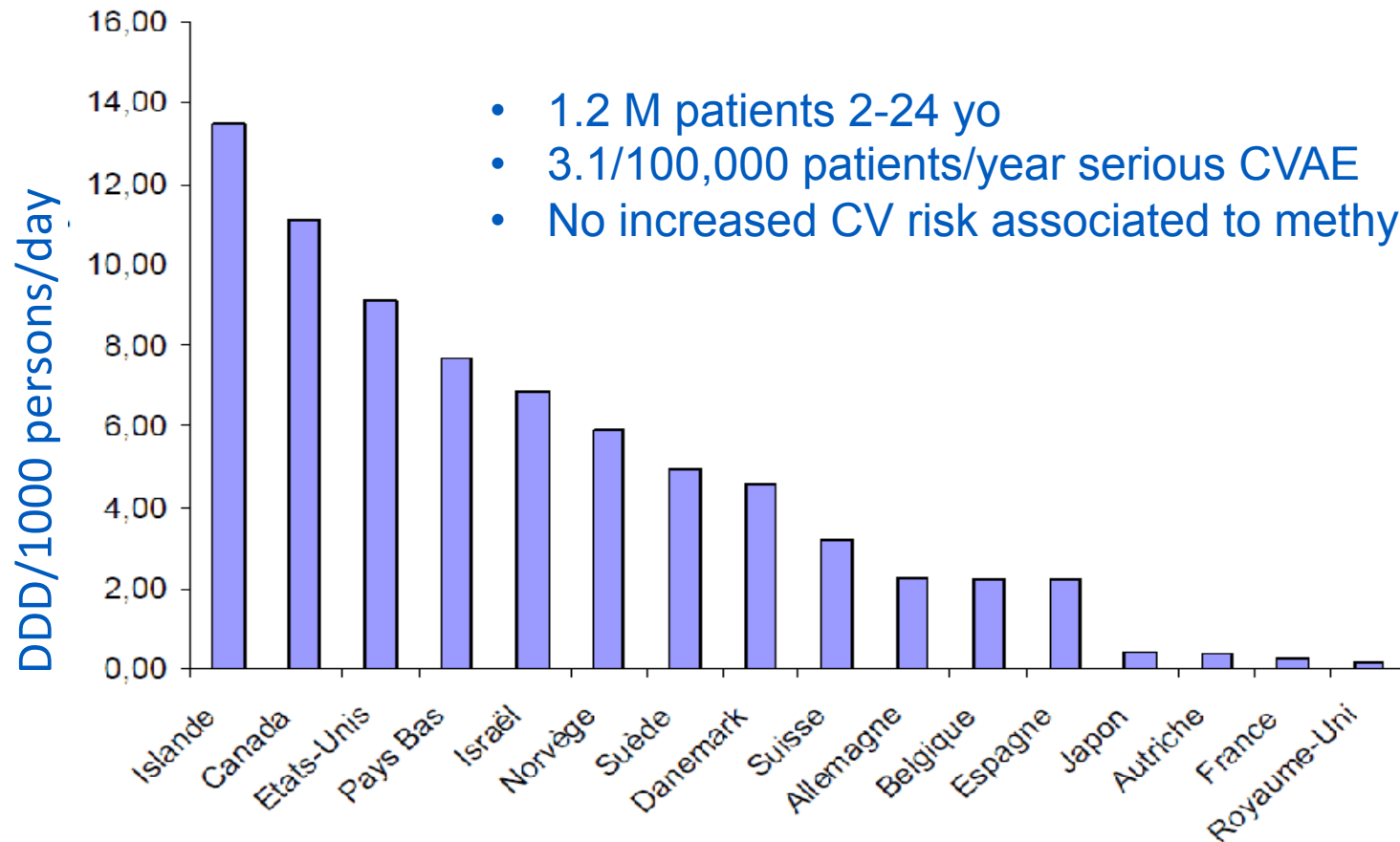
Spontaneous notifications of CV adverse events associated with so called « energy drinks » in France

CV adverse events 8-18 years old



Methylphenydate

Defined Daily Doses 2005-2011



- 1.2 M patients 2-24 yo
- 3.1/100,000 patients/year serious CVAE
- No increased CV risk associated to methylphenydate

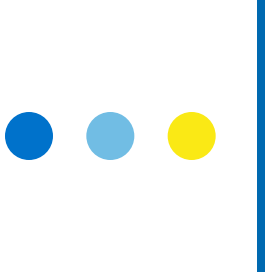
Intl Narcotics Control board. Psychotropic Substances - Technical Reports, Report 2012: Statistics for 2011

Cooper WO et al. 2011. N Engl J Med 365(20):1896-1904.

Elevated troponin in children

- Myocarditis or myopericarditis (22/32 cases) with abnormal
 - echo,
 - troponin
- Drugs more likely associated with vasospasm
 - 7/32 cases

Thankavel P. et al 2014. Cardiol Young (2) 283-89.

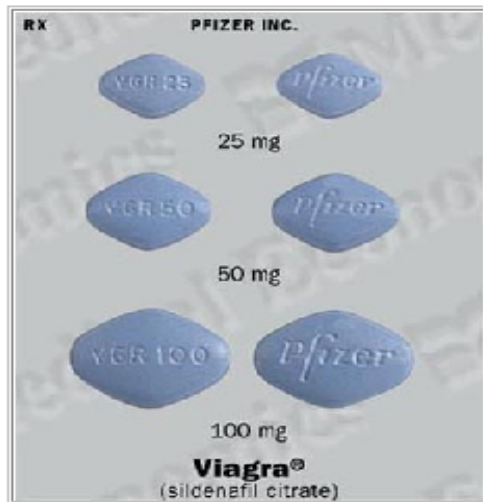


Médicaments « récréationnels »

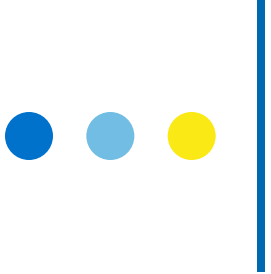
- Aggravent l'HTA
 - Ecstasy
 - Cocaïne
 - Crystal métamphétamine

Médicaments « récréationnels » et Poppers

- Dysfonction érectile : 40% > 60 ans
- Sildénafil



- Hypotension



Conclusion

- Ce ne sont pas des intoxications rares
- Difficiles à diagnostiquer (indétectable)
- Ischémie cardiaque
 - ↑ sympathomimétique, spasme coronarien
- Cardiologues doivent être “ en alerte ”
 - enfants/étudiants
 - douleur précordiale, tachycardie, ↑ PA
 - tableau anxieux, irritabilité, excitation, confusion, dépression voire violence...

Merci

A scenic photograph of a sunset over the sea. The sun is low on the horizon, creating a bright lens flare and reflecting on the water. Palm tree fronds are visible in the upper corners of the frame. The sky is a gradient of blue and orange.

<http://centre-pharmacovigilance-nice.fr>