Effects of Recreational Drugs on the Cardiovascular System

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Effects of Recreational Drugs on the Cardiovascular System

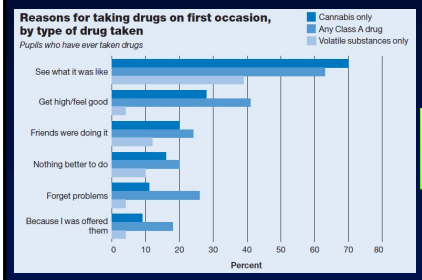
- Cocaine
- Amphetamine
- Cannabis
- Volatile Substances
- Narcotics

Deaths related to drug poisoning in England and Wales: 2015 registrations

- 3,674 drug poisoning deaths involving both legal and illegal drugs registered in England and Wales – 2015
- 2,479 (or 67%) were drug misuse deaths involving illegal drugs only.
- The mortality rate from drug misuse was the highest ever recorded, at 43.8 deaths per million population.
- Males were almost 3 times more likely to die from drug misuse than females (65.5 and 22.4 deaths per million population
- Deaths involving heroin and/or morphine doubled in the last 3 years to 1,201 in 2015, and are now the highest on record.
- Deaths involving cocaine reached an all time high in 2015 - 320 deaths
- People aged 30 to 39 had the highest mortality rate from drug misuse (98.4 deaths per million population), followed by people aged 40 to 49 (95.1 deaths per million).

National Centre for Social Research and the National Foundation for Educational Research

NHS The Information Centre for health and social care

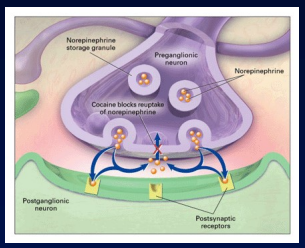


Smoking, drinking and drug use (11-15 years) among young people in England in 2009

Cocaine

- Cocaine hydrochloride= usual street preparation
- Freebase cocaine(cocaine alkaloid)= cocaine is extracted with alkaline (buffered ammonia) and solvent is added(acetone). Freebase pops or cracks when heated hence the term "crack"
- Rock of crack= cocaine hydrochloride heated with baking soda until a rock is formed-these are smoked in paraphernalia
- Speedball-heroin laced with cocaine-no narcan

Cocaine - Mechanism of Action



Cocaine blocks the presynaptic reuptake of NE and dopamine at sympathetic nerve terminals, producing an excess of these neurotransmitters at the postsynaptic receptor site.

NEJM, 345:351, 2001

Pharmacokinetics of Cocaine

TABLE 1. PHARMACOKINETICS OF COCAINE ACCORDING TO THE ROUTE OF ADMINISTRATION.

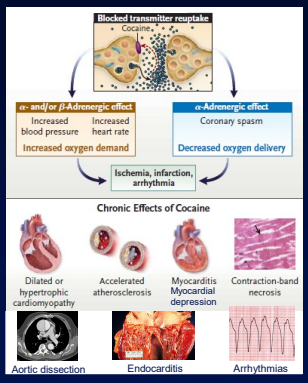
ROUTE OF ADMINISTRATION	ONSET OF ACTION	PEAK EFFECT	DURATION OF ACTION
Inhalation (smoking)	3–5 sec	1–3 min	5–15 min
Intravenous	10–60 sec	3–5 min	20–60 min
Intranasal or other mucosal	1–5 min	15–20 min	60–90 min

NEJM 2001;345:351

Metabolism of Cocaine

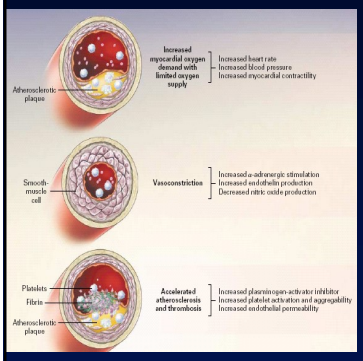
- Serum half life of 30-80 minutes
- Metabolised and excreted in the urine
- Cocaine can be detected in blood or urine only for several hours after its use
- Cocaine metabolites are detectable in urine for up to two weeks
- Hair analysis provides a very sensitive marker for cocaine use within the preceding weeks to months
- Combined with alcohol produces cocaethylene

Cardiovascular Effects of Cocaine



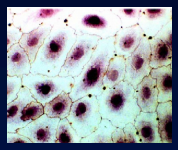
NEJM 2003;348 (6):487

Cocaine and Myocardial Ischaemia

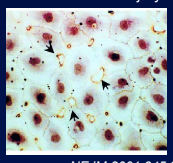


Accelerates atherosclerosis and vasospasm

Normal endothelium

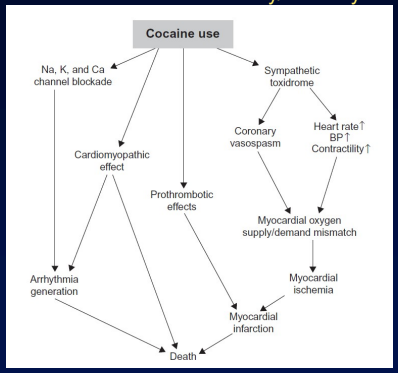


Cocaine-induced injury



NEJM 2001;345:351

The multifaceted way in which cocaine promotes myocardial ischaemia and morbidity/mortality



Ghuran and Francis. Cardiovascular Toxicity and Recreational Drugs in The Heart and Toxin. M. S. Ramachandran (Ed)

CARDIAC DYSRHYTHMIAS AND CONDUCTION DISTURBANCES REPORTED WITH COCAINE USE

Sympathetic Stimulation

Na Channel Blockade (1C)

K/Ca Channel Blockade

Metabolic acidosis

- Sinus tachycardia
- Sinus bradycardia
- Atrial fibrillation/atrial arrhythmias
- Supraventricular tachycardia
- Bundle-branch block
- Complete heart block
- Accelerated idioventricular rhythm
- Ventricular tachycardia
- Ventricular fibrillation
- Asystole
- Torsade de pointes
- Brugada pattern

CARDIAC ARRHYTHMIAS AND COCAINE

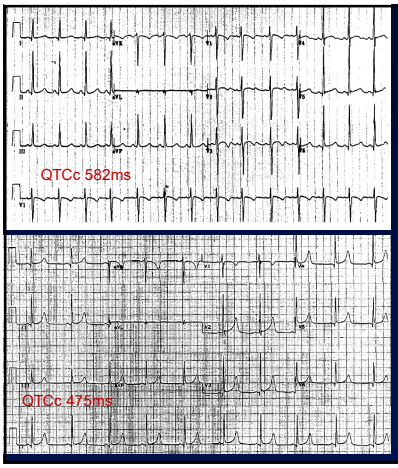
Electrophysiological effects of the Sympathetic Stimulation

- Shifts pacemaker from sinus node to junctional region
- Increases Purkinje fibre automaticity
- Alters P wave morphology and QT interval
- Shortens PR interval
- Increase after-depolarisations (facilitating triggered activity)
- Enhances re-entry during acute myocardial ischaemia
- Decreases ventricular fibrillation threshold

⬇

- Sinus tachycardia
- Supraventricular tachycardia
- Accelerated idioventricular rhythm
- Ventricular tachycardia and fibrillation
- Torsade de pointes

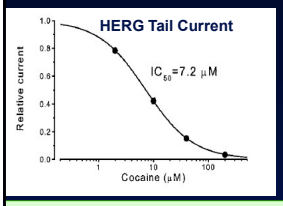
COCAINE and QT prolongation

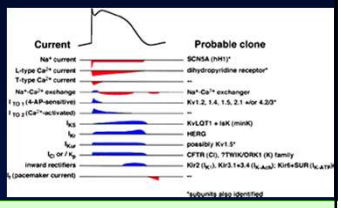


17 yr. old girl following cocaine binge.

Perera et al. Journal of Electrocardiology 1997;30:337-39

CARDIAC ARRHYTHMIAS AND COCAINE





Cocaine Blocks HERG but Not KvLQT11minK Potassium Channels

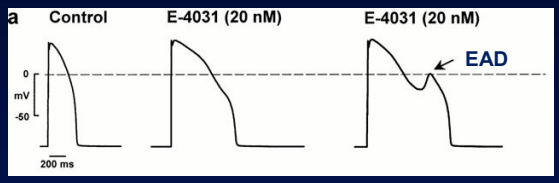
Greater block:
- Combined alcohol consumption (cocaethylene)
- Other QT prolonging drugs e.g methadone
- Predisposing conditions such e.g. congenital LQTS, electrolyte abnormalities, low repolarisation reserve

Cocaine effect on $I_{Ca,L}$ is complex with both inhibitory and stimulatory effects

Zhang et al. Mol Pharmacol 59:1069–1076, 2001

CARDIAC ARRHYTHMIAS AND COCAINE

Cocaine can increase the intracellular calcium concentration, which may result in afterdepolarizations and triggered ventricular arrhythmias



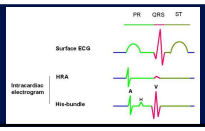
EAD Induced by IKr (HERG) inhibition by E-4031 in rabbit ventricular AP

Studenik, Zhou, January Br. J. Pharm. 2001

CARDIAC ARRHYTHMIAS AND COCAINE

	Infusion time (s)	QRS duration (ms)	MBPR (mm Hg)	MBPF (mm Hg)	HV interval (ms)	VERP (ms)	VFT (mA)
Coc–Placebo							
Baseline	0	32.86 ± 3.8	101.4 ± 26.9	101.4 ± 26.9	24.1 ± 5.1	148.7 ± 16.5	52.0 ± 18.2
Max change after inf.	487.7 ± 117	6.8. ± 1.8[a]	10.5 ± 6.9[a]	−30.5 ± 5.2[a]	5.0 ± 3.2[a]	17.6 ± 11.4[a]	−7.5 ± 3.7[a]
Coc+Sch							
Baseline	0	33.64 ± 4.1	97.9 ± 19.8	97.9 ± 19.8	24.6 ± 6.1	149.1 ± 11.4	39.2 ± 10.4
Max change after inf.	495.0 ± 103	6.07 ± 0.8[a]	12.2 ± 10.7[a]	−16.4 ± 13[a]	3.3 ± 3.5[a]	13.7 ± 7.7[a]	5.8 ± 08.7

Values expressed as mean ± SD.
MBPR, mean blood pressure rise; MBPF, mean blood pressure fall; HV, His–ventricular; VERP, ventricular effective refractory period; VFT, ventricular fibrillation threshold; Coc+Placebo, all 14 dgs with 5 days' treatment with placebo before cocaine infusion; Coc+Sch, the same 14 dogs with 5 days' treatment with SCH 39166 before cocaine ifusion; VFT, the 12 dogs who underwent VFT testing on day 2, six dogs in each group.
[a] $p < 0.01$ from baseline.



Kanani et al. Journal of Cardiovascular Pharmacology 1998;32:42-48

2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

7.10. Cocaine and Methamphetamine Users: Recommendations

CLASS I

1. Patients with NSTE-ACS and a recent history of cocaine or methamphetamine use should be treated in the same manner as patients without cocaine- or methamphetamine-related NSTE-ACS. The only exception is in patients with signs of acute intoxication (e.g., euphoria, tachycardia, and/or hypertension) and beta-blocker use, unless patients are receiving coronary vasodilator therapy. *(Level of Evidence: C)*

CLASS IIa

1. Benzodiazepines alone or in combination with nitroglycerin are reasonable for management of hypertension and tachycardia in patients with NSTE-ACS and signs of acute cocaine or methamphetamine intoxication (741-744). *(Level of Evidence: C)*

CLASS III: HARM

1. Beta blockers should not be administered to patients with ACS with a recent history of cocaine or methamphetamine use who demonstrate signs of acute intoxication due to the risk of potentiating coronary spasm. *(Level of Evidence: C)*

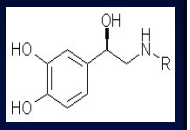
Treatment of Cocaine Related Arrhythmias

- Supportive as short ½ life
- Benzodiazepines
- Treat myocardial ischaemia
- Correct hypoxia, metabolic and electrolyte disturbances
- Temporary wire if significant bradyarrhythmias
- DCC for haemodynamic tachyarrhythmias
- Adenosine for SVT, verapamil provided no HF
- Ventricular arrhythmias- lidocaine, Mg, Amiodarone
- ?Bicarbonate

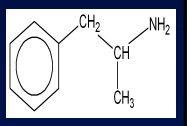
Amphetamines Ecstasy

Routes of use
- Oral
- Nasal
- Intravenous

Adrenaline

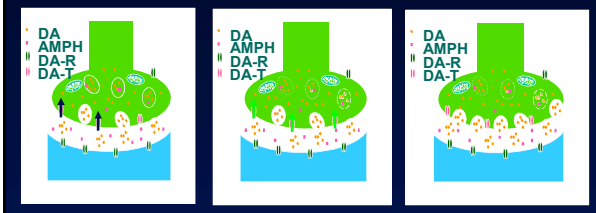


Amphetamine



Structure resembles natural neurotransmitters of Epi, DA

Amphetamines

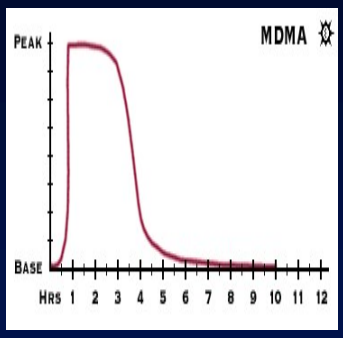


AMPH enters pre-synaptic vesicles

↑ release of DA in pre-synapse

↑ DA in pre-synapse and synapse

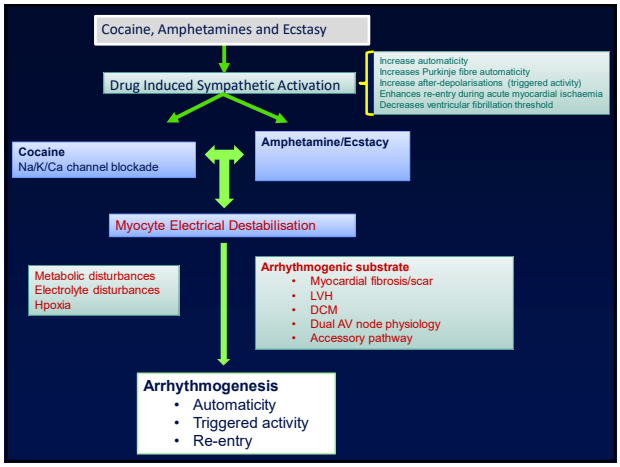
Pharmacokinetics



Onset	20-90 min
Rise up	5-20 min
Plateau	2-3 hours
Come down	1-2 hours
After Effects	3-24 hrs
Half-life	12-13 hours

Cardiovascular Effects of Amphetamines

- HTN and tachycardia
- Hypotension- central ANS depression/catecholamine depression
- Myocardial ischaemia/infarction and CVA
- Catecholamine induced myocyte necrosis
- Cardiac dysrhythmias - supra/ventricular tachyarrhythmias
- Acute heart failure, cardiomyopathy
- Non-cardiogenic pulmonary edema
- Aortic dissection, endocarditis
- Petechial and major hemorrhages – intracranial, retinal and other organs
- Necrotising vasculitis
- Pulmonary hypertension



Treatment of Amphetamine/Ecstasy Related Arrhythmias

- Similar principles to cocaine
- Benzodiazepines
- Treat myocardial ischaemia
- Correct hypoxia, metabolic and electrolyte disturbances
- DCC for haemodynamic tachyarrhythmias
- Adenosine for SVT
- Ventricular arrhythmias- lidocaine, amiodarone?, Mg
- ? Forced acid diuresis (opposite to cocaine)

Cannabis/Marijuana

Pharmacologically active substance = delta-9-tetrahydrocannabinol (A-9-THC)

Smoked – rapidly absorbed through the lungs

Ingested- slower and less predictable

Physiological effects persists btw. 4-6 hours

Plasma half-life 20-30hrs

Detected in urine for several days- occasional users vs several months in chronic users

Cannabis/Marijuana

Biphasic effect on the autonomic nervous system

Low or moderate doses

- ↑sympathetic activity, ↓ parasympathetic activity
- tachycardia and ↑cardiac output ?↑BP
- smooth muscle vasodilator, ? ↓ BP

High doses or chronic use

- ↓ sympathetic activity, ↑parasympathetic activity
- tachycardia and hypotension

Ghuran, Malik in: Clinical Guide to Cardiac Autonomic Tests. Kluwer Acad Publishers

Cannabis/Marijuana and the ECG

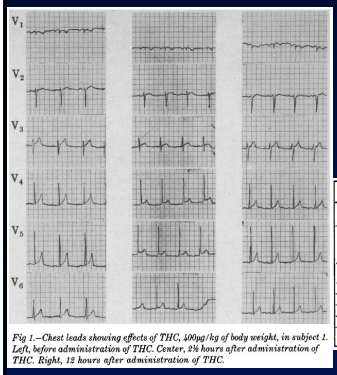


Fig 1.—Chest leads showing effects of THC, 400μg/kg of body weight, in subject 1. Left, before administration of THC. Center, 2¼ hours after administration of THC. Right, 12 hours after administration of THC.

Reversible changes: P wave, T wave, ST segment

? independent effect or related to heart rate

Increase in SVE, VE

1st and 2nd degree heart block

Electrocardiographic Changes 2½ Hours After Drug Administration

Subject No.	THC*† Small Dose‡	THC*† Large Dose§
1	Slight increase in heart rate; S-T-segment elevation in leads II and III	Increase in heart rate; S-T-segment elevation in chest leads; T-wave flattening in all leads
2	T-wave flattening in all leads	Slight increase in heart rate; T-wave flattening in limb leads
3	No change	No change
4	No change	Slight increase in heart rate
5	No change	Increase in heart rate
6	No change	Increase in heart rate
7	No change	Slight increase in heart rate; PVCs, 5/min

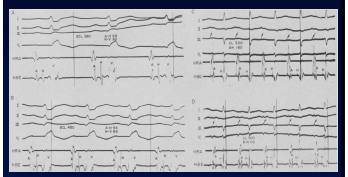
Kochar et al. JAMA 1973;225:25-7

Table III. Summary of electrophysiologic findings after administration of Δ-9-THC

	N	State	Mean ± SEM	p value
Sinus cycle length (msec.)	6	C*	785 ± 76	< 0.01
		THC	563 ± 42	
SRT (msec.)	6	C	943 ± 84	< 0.005
		THC	617 ± 40	
Max SRT (msec.)	6	C	1060 ± 99	< 0.005
		THC	690 ± 49	
SACT (msec.)	6	C	77 ± 8.9	< 0.005
		THC	56 ± 9.7	
P-A interval (msec.)	6	C	29 ± 2.9	NS
		THC	28 ± 3.9	
Atrial ERP (msec.) (NSR)	6	C	212 ± 16.4	NS
		THC	197 ± 17	
Atrial FRP (msec.) (NSR)	6	C	293 ± 19	NS
		THC	261 ± 14.7	
Atrial ERP (msec.) (during atrial driving)	6	C	216 ± 14	NS
		THC	193 ± 17.4	
Atrial FRP (msec.) (during atrial driving)	6	C	252 ± 11.4	NS
		THC	240 ± 19.5	
A-H Interval (msec.) (NSR)	6	C	81 ± 5.4	< 0.02
		THC	71 ± 4.9	
A-H Interval at equivalent cycle length (msec.)	5	C	118 ± 17.2	< 0.05
		THC	78 ± 9.3	
Paced atrial rate producing 2° A-V block (beats/min.)	6	C	163 ± 17	< 0.05
		THC	188 ± 9.4	
A-V nodal ERP (msec.) (NSR)	6	C	330 ± 26.7	< 0.05
		THC	270 ± 15.9	
A-V nodal FRP (msec.) (NSR)	6	C	427 ± 28.9	< 0.005
		THC	348 ± 25.9	
A-V nodal ERP (msec.) (during atrial driving)	6	C	367 ± 46.4	< 0.025
		THC	285 ± 25.6	
A-V nodal FRP (msec.) (during atrial driving)	6	C	433 ± 43.9	< 0.02
		THC	368 ± 32.8	
H-V interval (msec.)	6	C	39 ± 4.3	NS
		THC	38 ± 4.5	

*Abbreviations: C = control; ERP = effective refractory period; FRP = functional refractory period; Max = maximum; msec. = millisecond; N = number of patients; NS = not significant; SACT = sinoatrial conduction time; SEM = standard error of the mean; SRT = sinus node recovery time; THC = Δ-9-tetrahydrocannabinol (cannabis); NSR = normal sinus rhythm.

Marijuana and Electrophysiology



- Δ-9-THC markedly enhanced sinus automaticity and facilitated sinoatrial and A-V nodal conduction
- Intra-atrial and intraventricular conduction seems to be unaffected by THC

Miller et al. Am Heart J 1977;94:740-747

Marijuana and Arrhythmias

Sympathetic stimulation ⟷ Parasympathetic stimulation

↓Atrial repolarisation

Predisposing Substrate

Hypertension

Cardiac ischaemia
- Microvascular level
- Coronary spasm
- Carboxyhaemoglobin

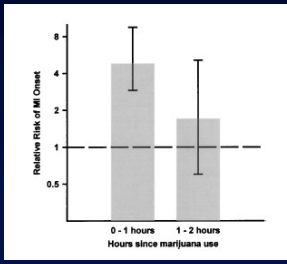
Atrial flutter and fibrillation – case reports

???? Ventricular arrhythmias

Fisher, Ghuran et al. Emerg Med J 2005; 22: 679-80

Marijuana and Myocardial Ischaemia

5 fold increase of a MI within 60 minutes of marijuana use



Exercise time to angina

Decreased by 48% after a single marijuana cigarette

Decreased by 8.6% decrease after placebo

Decreased by 23% after smoking a high nicotine tobacco cigarette

Mittleman et al. ***Circulation. 2001;103:2805-2809***

Volatile Substances Abuse

- **"Sniffing":** inhaling *raw* vapors.
- **"Huffing":** inhaling vapors from a *soaked cloth* held next to mouth or nose.
- **"Bagging":** inhaling vapors from a *bag*, balloon, or other vessel which is then held over mouth or nose.

UK 3.5-5% adolescents
- Legal
- Cheap
- Widely available

Demographic - VSA

- Males > Females
- Peak age: 13-19 yr.
- Lower socioeconomic status
- Poor school performance
- Family dysfunction

- **Chemicals can be detected in blood if samples are obtained within 10 hours of exposure.**
- **Urine analysis for metabolites may extend the detection time: toulene, tylene and chlorinated solvents**

Volatile Hydrocarbons/Solvents

US poison centres from 1996 to 2001

Categories, examples and chemicals present in commonly abused inhalants

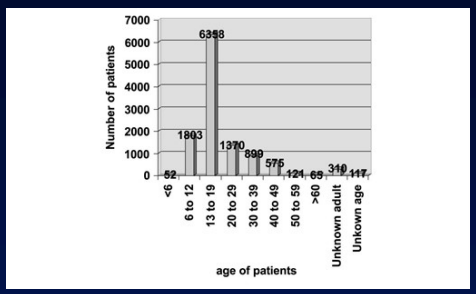
Category	Examples	Chemicals	Other terms
Aliphatic, aromatic and halogenated hydrocarbons	Hair spray, air fresheners, deodorants	Butane, propane, fluorocarbons	Medusa, moon gas, poor man's pot, air blast, discorama, hippie crack, chroming, gladding, whiteout
	Fuels including cigarette lighters	Gasoline, propane, benzene, butane	
	Paint/polish removers, paint thinners, felt-tip markers, correction fluids, glues and rubber cements	Trichloroethane, trichloroethylene, toluene, hexane, acetone, methylene chloride, ethyl acetate	
	Varnishes, lacquers, resins, lacquer thinners	Benzene, xylene	
	Dry cleaning fluids, spot removers, degreasers	Trichloroethane, tetrachloroethylene, xylene	
	Computer/electronics cleaning sprays	Dimethyl ether, hydrofluorocarbons, hydrocarbons	
		Hydrocarbons	

Table 1. Top 10 categories of volatile substances abused and their associated outcomes (1996–2001).

Category	Number of cases	Percent of total cases	Number of serious cases	Serious as a percent of category	Number of fatalities	Percent of total fatalities
Hydrocarbons (includes gasoline)	4470	40.6%	989	22.1%	29	44.6%
Paints	1450	13.2%	341	23.5%	1	1.5%
Gases (propane, butane, etc.)	630	5.7%	128	20.3%	7	10.8%
Air fresheners	620	5.7%	99	16%	17	26.2%
Formalin	598	5.4%	140	23.4%	2	3.1%
Home cleaning substances	566	5.1%	82	14.5%	2	3.1%
Personal care products	516	4.7%	36	7%	2	3.1%
Adhesives	512	4.7%	108	21.1%	2	3.1%
Arts/crafts products	490	4.5%	37	7.6%	0	0
Auto products (excludes gasoline)	487	4.4%	146	30%	3	4.6%

JF Williams et al. Paediatrics 2007 May;119(5):1009-17. *HA Spiller et al* Am J Drug Alcohol Abuse 2004;30:155-65.

VSA



HA Spiller et al Am J Drug Alcohol Abuse 2004;30:155-65

VSA - Acute Cardiovascular Effects

Tachyarrhythmias – SVT, Atrial fibrillation, VT/VF

Myocardial sensitization to catecholamines

- Mostly with Solvents/HCs
- Δ in cellular membrane function/transmembrane ion conductance
- ↑ incidence of epinephrine-induced dysrhythmia in rats exposed to VSAs
- Direct VSA-induced ↑ in endogenous catecholamines
- ↑ automatcity in Purkinje fibres
- Decreased contractility
- Specific idiosyncratic effects
  - toulene can inhibit sodium channels, ↑ QRS/QTc, myocarditis
  - hexane ↓ VF threshold

A Ghuran, J Nolan. Heart 2001;627-633, Y Lessard et al. Cardivasc Res 1986;20:807

Sudden Sniffing Death

- Mechanism of Death
  - *Induce **V-fib**.*
    Most frequently with *toluene* and *halogenated HCs:*

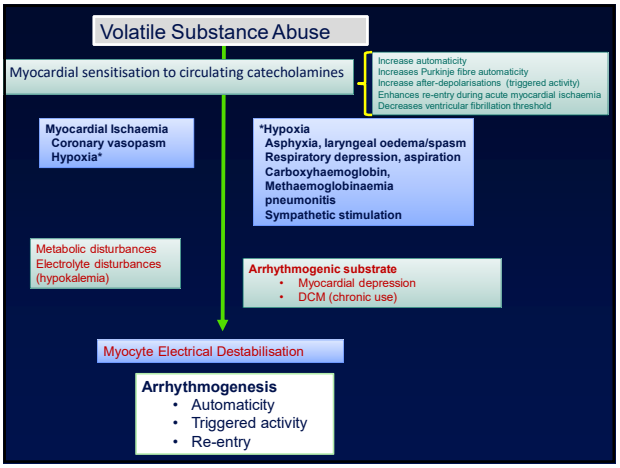
VSA- Acute Cardiovascular Effects

Bradyarrhythimias

- ↓ sinoatrial node automaticity, ↑ PR interval, AV block (animals)
- Intense vagal stimulation – volatile substance sprayed directly into the oral cavity.
- Asystole → secondary ventricular arrhythmias

Hypotension

- Some Volatile substances- structurally related to general anaesthesia
- Decreased contractility



VSA - Management

- **ABCs/ACLS**
- **Remove exposure**
- **Decontaminate skin/eyes**
- **Managed in a calm non-threatening environment with sedation if necessary**
- **Correct hypoxia, metabolic and electrolyte disturbances**
- **Hypotension – IV fluids (caution with myocardial depression)**
- **Calcium administration may help with myocardial depression**
- **Bradyarrhythmias – temporary pacing, (cautiously with atropine)**
- **Tachyarrhythmias – beta blockers or amiodarone, DCC**
- **Myocardial ischaemia – usual protocol.**

VSA - Management

Specific Therapies

- Amyl Nitrite
  - Methylene Blue for Methemoglobinemia
- Hepatic/Renal Toxicity (Chloroform, TCE, TC-Ethylene)
  - N-Acetylcysteine
- Methylene Chloride (dichloromethane)
  - 100% O_2 ?hyperbaric oxygen therapy

The Guardian 24th September 2011


Pair who slept as their children walked alone on A38 are spared jail

Girl, 2, and boy, 4, rescued from road by passing driver

Young parents punished for child cruelty offences

Helen Carter

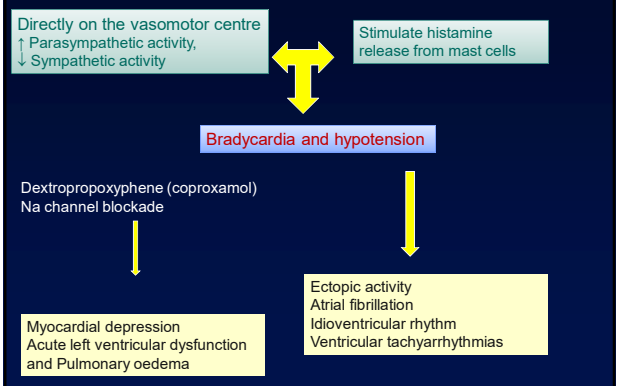
VSA
Morbidity and Mortality by Proxy

Opioids – Diamorphine/morphine

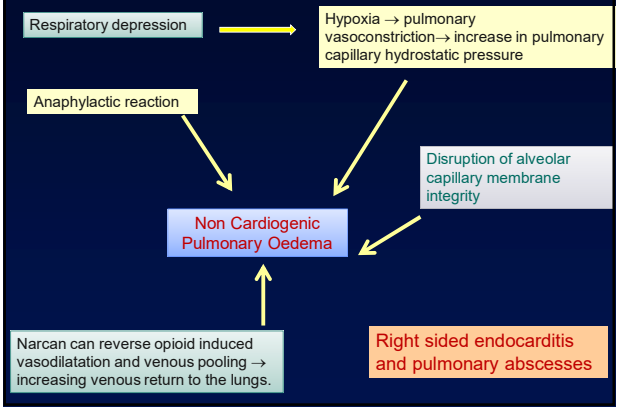
Injected, smoked, or ingested orally

Morphine - Plasma half life of two to three hours.
- Undergoes rapid hepatic metabolism, metabolites excreted in the urine.
- Metabolites can be detected for up to 48 hours in occasional users, several days chronic users.

Opioids – Diamorphine/morphine



Opioids – Diamorphine/morphine



Conclusion

Recreational Drug use continues to be a major problem across all age groups and social classes

Some of these agents can induce major acute changes in cardiovascular function and chronic use may also cause irreversible damage to the heart

Polydrug use and combined alcohol ingestion can have synergistic detrimental effects on the cardiovascular system

Many patients will be unable or unwilling to admit to recreational drug use and therefore a high index of suspicion is required.

The key to successful management is early recognition and appropriate intervention.