

PSYC1022- Psychology of Addiction

LECTURE 1 + 2- ORIGINS AND MANUFACTURE OF DRUGS

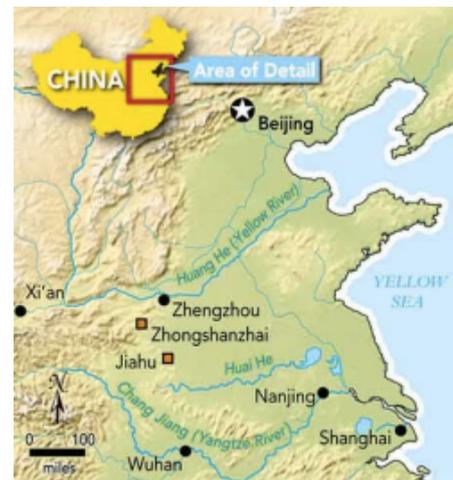
DRUG CLASSIFICATIONS

- Drugs can be used classified in many ways:
 - Licit- Legal
 - Illicit- Illegal
 - Based on their effect on the Central Nervous System (CNS).
- One method involves classification based on the drug's CNS effects
 1. Depressants: Slow down CNS activity
 2. Stimulants: Speed up CNS activity
 3. Hallucinogens: Alter sensory perceptions (psychotogenic) by interfering with CNS signalling
 4. Other: Substances that fit into several categories as there are different experiences across individuals. Also, includes drugs that have more than one effect on the body and CNS.

DEPRESSANTS:

ALCOHOL containing liquid can be simply created by leaving fruit in a container for some period of time. Consume liquid to experience the drugs' effect.

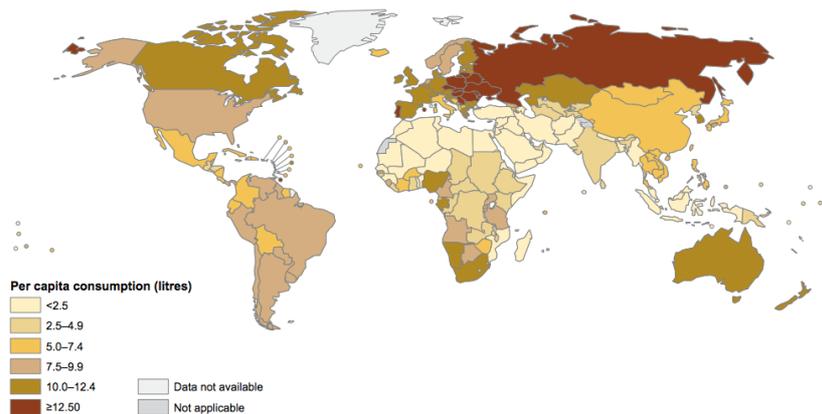
- It has been conjectured that alcohol was consumed by Palaeolithic humans may have consumed alcohol but there is little direct evidence.
- The first direct evidence of alcohol production comes from an archaeological site in **Jehu, China** where pots dating from **7000-5800BC** (Neolithic period) were found to find the residue of an alcoholic liquid made from fermented rice, honey & hawthorn.
- "Chateau Jiahu" which has been reverse engineered from molecular archaeology. Alcohol made from rice flakes, wildflower honey, Muscat grapes, hawthorn fruit with barley malt & fermented with a sake yeast.



- **4100BC: Areni-1 Cave, Armenia**- one of the earliest known sites of wine production.
- The press sits inside the cave and is slanted downwards towards the mouth of a large jar inserted in the platform's edge to catch the crushed grape juice. This same design of wine press was common throughout the Mediterranean till 1900.

- Today, alcohol is globally available.
- According to report in 2014 from WHO:
 - Worldwide consumption is 6.2 L of pure alcohol per person above 15 years old.
 - Higher the economic wealth of a country the higher the consumption of alcohol.
 - Highest rates in Europe, Russian Federation, Australia, Canada
 - Unrecorded (i.e. home-brewed liquor) is thought to account for almost 25% of worldwide consumption
 - 3.3 million deaths worldwide are attributable to alcohol consumption

Figure 2. Total alcohol per capita consumption (15+ years; in litres of pure alcohol), 2010



OPIUM is derived from the sap of the opium poppy seed head, which is released following tissue damage and acts as an anti-herbivore chemical.

- Great care is taken to choose the time for making incisions into the poppy seed head so neither rain, wind and dew can spoil the sap, so weather considerations are important for choosing when to make incisions. Sap is then collected and the opium brick is then typically sold by the farmer to the broker.
- In ancient times, opium was the end product but more recently, brokers supply the opium to refiners who convert it into a more transportable morphine brick or heroine powder.
- Selective breeding has yielded an opium poppy that has substantially higher concentrations of opioids than the wild variant. Most commonly grown today.
- Opium was used throughout broadly throughout Europe, Asia, Middle East & North Africa during the Neolithic age (10,000 -2000BC). There are numerous archaeological sites of opium poppy seed pods buried in a ritual or sacred context. For Example:
 - 4200BC Brittany, France- ceramic bowls found in a sacred site
 - Southern Spain- globular glass bags of opium capsules found in a burial site



Numerous major earlier civilisations have also left written records of opium use:

- **1500 BC: The Ebers Papyrus**

- is believed to have been copied from earlier texts (**Circa 3400 BC**)
- found between the legs of a mummy in a tomb near Luxor, Egypt
- **1872:** Purchased by Professor Ebers
- The papyrus describes a mixture of opium and another material which was found effective in quietening crying children.
- some time ago children in Egypt, India and Europe were being soothed with opium. It is said that mothers often laced their nipples with poppy juice so that the child would immediately stop crying upon sucking the 'drugged' milk.
- **1332-1323 BC:** Cultivation and trade of opium was in full operation during the reign of King Tutankhamun- contributed significantly to the wealth of the Egyptian pharaohs.
- **700 BC: Homer's 'The Odyssey'**
 - Opium recreational use described: Telemachus is depressed after failing to find his father Odysseus. But then Helen, "...had a happy thought. Into the bowl in which their wine was mixed, she slipped a drug that had the power of robbing grief and anger of their sting and banishing all painful memories. No one who swallowed this dissolved in their wine could shed a single tear that day, even for the death of his mother or father, or if they put his brother or his own son to the sword and he were there to see it done..."
 - Opium's ability to rid the body of pain and give the body an intense feeling of euphoria – this is what makes heroine so addictive.

MORPHINE was isolated by the German pharmacist, Friedrich Sertürner in 1803. Sertürner named it after Morpheus, the Greek God of dreams.

- Morphine crystals were added to food to kill unwanted rats and dogs in the town. He observed in these animals that morphine evoked sleep and eventually death.
- He suffered from gout in his later life & quelled his pain with the very morphine he had isolated.
- The alkaloid morphine is generally 8 to 14% of the dry weight of opium.
- Sertürner's Morphine extraction method still used in illicit labs.
- It takes a full day to extract 'pure' morphine from opium.

LAUDANUM

- **1493-1541: Paracelsus**, a Swiss-German occultist discovered that opium could be better dissolved into a solution of alcohol than water.
 - He named that solution Laudanum (AKA tincture of opium)
 - He added a variety of ingredients such as garlic & frog spawn
 - Although useful for pain reduction, the compound was largely ignored.
- **1624-1689: Thomas Sydenham**, English physician produced & promoted his own Laudanum recipe which could be used as a cure for a range of medical conditions. His recipe included: 1 Pt Canary Island wine, 2 Oz strained opium, 1 Oz saffron.
- **1837-1901:** use continued in Victorian England & USA
- especially by women
- Laudanum remains available by prescription in these countries although therapeutic applications are generally restricted to pain relief & alleviating withdrawal symptoms in babies born to heroin or opiate addicted mothers
- **1910 onwards:** increasingly restrictive laws established which regulated the production and sale of addictive compounds including Laudanum.

CODEINE is an alkaloid (like morphine) present in morphine at a concentration of about 1-3%.

- **1821: Pierre Robiquet** (French chemist) isolated from morphine using the process of Omethylation (substitution of an atom by a methyl group).
- It is the most widely used opiate in the world and has an excellent safety record
- It is used as an analgesic (pain), antitussive (coughing), antidiarrheal, antihypertensive (blood pressure), antianxiety, sedative, to suppress premature labor contractions and myocardial infarction (heart attack).
- It does have addictive potential but is less potent than morphine or heroin.

HEROIN (diacetylmorphine): first synthesised by English chemist, **Charles Wright** in **1874**.

- He accidentally boiled morphine and acetic acid, over a stove for several hours. This process of acetylation introduces an acetyl group into the compound.
- The modern technique of producing heroin entails a complicated series of steps in a good laboratory:
 1. equal quantities of morphine and acetic acid are heated in a glass or enamel-lined container for six hours at 85C. The morphine and the acid combine to form impure diacetylmorphine.
 2. water and chloroform are added to the solution to precipitate impurities. The solution is drained & sodium carbonate added to make the heroin solidify and sink.
 3. heroin is filtered out of the sodium carbonate solution with activated charcoal and purified with alcohol. This solution is gently heated to evaporate the alcohol and leave heroin, which may be purified further.
 4. Purification in the fourth stage, involving ether and hydrochloric acid, is notoriously risky as the volatile ether gas may ignite & produce a violent explosion. The final product is a fluffy, white powder known in the trade as number four (pure) heroin.
- **1898: Felix Hoffman, German physicist** discovered the same process 23 years later.
- He worked at Bayer & discovered aspirin by subjecting salicylic acid to the same acetylation process that Charles Wright had applied to morphine.
- Hoffmann replicated this procedure & named the resulting diacetylmorphine, heroin, in reference to its heroic effects
- Bayer marketed heroin as an effective sedative for coughs, like morphine, but without the addictive potential
- Sales rocketed and widespread dependence followed
- In **1913**, Bayer ceased production with the introduction of widespread legislation to control the production and sale of such compounds.

STIMULANTS:

TABACCO (Nicotine) was smoked by tribes across the Americas. It was discovered by Christopher Columbus in 12 October 1492, when he landed in San Salvador Island in the Bahamas. Scouts reported tribes people smoking "half-burned wood in their hands."

- In **1492: Rodrigo de Jerez** was known to be the first European smoker. In November 1492, he observed the San Salvador natives smoking and picked up the habit, which he then introduced to his friends in his hometown, Ayamonte, Spain. The Spanish Inquisition imprisoned him for his “sinful and infernal habits.” He was released 7 years later when smoking had caught on.
- **1523:** Tobacco merchant of Lisbon officially documented- showing how quickly the trade of tobacco leaf had been established.
- **1604: Stuart King James I** denounced tobacco use as “harmful to the brain, dangerous to the lungs.”
- **1604:** English introduce heavy tariffs on tobacco imports beginning the perverse financial relationship between the state and tobacco merchants.
- **1609:** Commercial production began in Jamestown, Virginia from tobacco imported from Bermuda
- **Until 1883:** Tobacco excise tax accounted for one-third of the internal revenue collected by the US government.
- In **1962, Britain’s Royal College of Physicians:** Published causal link between smoking & lung cancer, bronchitis and cardiovascular disease
- It is now broadly recognised by governments that quit smoking interventions yield substantial long term profits resulting from reduced health care expenditure & more productive economic activity. Thus, the short-term reduction in tax revenues are more than compensated for by long term profits. This economic argument underpins developed countries’ sustained policies for reducing smoking
- Nicotine constitutes approx. 0.6-3% of the dry weight of tobacco leaf with biosynthesis that takes place in the roots and accumulates in the leaves.
- Nicotine functions as an anti-herbivore chemical. It is a potent neurotoxin, particularly to insects. E.g. application of nicotine to plant material repels the Western Flower Thrip (amongst others).
- Nicotine derivative compounds widely used as pesticides in agriculture to reduce plant damage

COCAINE is an alkaloid (like nicotine and the opiate alkaloids). It is derived from the leaves of the coca plant and acts as an anti-herbivore chemical. Cocaine grow naturally in abundance in South America.

- Paleo botanical evidence, as well as archaeological artefacts indicate that Coca leaves were consumed by natives of Venezuela, Colombia, Ecuador, Peru, Bolivia & North Argentina. These regions are areas where the plant grows naturally in abundance.
- Evidence includes:
- **1000 BC:** Mummies found in Northern Chile showed the presence of cocaine
- **6000 BC:** Evidence of coca leaf & lime production & distribution in Nanchoc Valley, Peru
- Tea infusions (often with an alkaline substance such as lime to help release the psychoactive alkaloids) or chewed leaves were consumed by South American natives. This is still legal in Peru and Bolivia and is widely practiced by natives in other South American countries despite prohibition
- **1500s:** Spanish conquistadors landed in South America where they initially dismissed coca leaf consumption as the ‘Devils work’ but soon came to commercialise & tax its

distribution when they discovered that the enslaved native population worked harder under its influence.

- It was introduced in Spain by the **1600s** but did not become popular until the Italian neurologist, **Paolo Mantegazza**, published a report in **1858** which highlighted the cognitive enhancing effects of coca leaf infusions. This led to several commercial wine products containing coca infusions.
- The US state of Georgia introduced alcohol prohibitions in **1886**. **John Pemberton**, US Pharmacist, developed a non-alcoholic recipe with sweet syrup & coca infusion, known as Coca-Cola.
- **1904**: Cocaine is extracted from the Coca-Cola recipe following the prohibition of cocaine.
- The cocaine alkaloid was first isolated in **1855** by German chemist, **Friedrich Gaedcke** who named it “erythroxyline.”
- In 1860, Albert Niemann published his PhD thesis in which he described a better extraction process, which is the basis of the contemporary technique. He described its anaesthetic effects, which is reduction in touch sensation, and named it cocaine.
- 3 steps of Niemann’s technique are used by South American drug cartels for illicit production:
 1. Coca paste: Place macerated leaves in a 55-gallon drum & cover with water. Add kerosene (a solvent) & mix vigorously by hand or place in washing machine or cement mixer to dissolve the water insoluble cocaine alkaloid, then filter off leaf waste & retain the solution. Add dilute sulfuric acid to turn the cocaine into water soluble cocaine sulfate, then add lime to precipitate coca paste as a yellow solid. Remove & package the paste.
 2. Coke base: Dissolve coca paste in dilute sulfuric acid. Carefully add the oxidizing agent potassium permanganate and stir vigorously to precipitate remaining impurities as a black sludge leaving overlying solution clear. Filter & add ammonia to precipitate pure coke base.
 3. Cocaine hydrochloride: Dissolve coke base in diethyl ether to precipitate remaining impurities. Filter solution and stir in an equal volume of acetone & hydrochloric acid which immediately precipitates cocaine hydrochloride as shiny white, flaky crystals. Filter & dry under heat-lamps and/or microwave ovens, press, package & ship.

Types of Cocaine:

- Cocaine Hydrochloride: is injected, snorted or taken orally. It is not smoked because it will not vaporize until about 197°C. This burns & destroys the alkaloid giving a weak high plus a foul taste.
- Freebase Cocaine: is made by dissolving cocaine hydrochloride in water, diethyl ether and ammonia, then extracting the precipitate. Freebase vaporises at 98°C, so it can be smoked, giving this form a faster high. However, diethyl ether is highly flammable in production & residual ammonia is damaging to the lungs.
- Crack Cocaine: devised to enable smoking without the problems of a freebase. Crack is made by dissolving cocaine hydrochloride in water and sodium bicarbonate (baking powder) to form the crystallised precipitate. It crackles when smoked giving its name. this is a potentially addictive substance.

AMPHETAMINE derived from the plant Ephedra which grows throughout the world. • This plant has long been used in Chinese medicine for the treatment of asthma, hay fever & colds.

- **1885:** Japanese organic chemist, **Nagai Nagayoshi** extracted the sympathomimetic amine, ephedrine, from ephedra. It was used as a decongestant (clear blocked nose) & to stop asthma attacks (preferable to an injection of adrenalin used at the time).
- **1887:** Amphetamine was first synthesized by Romanian chemist **Lazăr Edeleanu**, in an attempt to make a synthetic ephedrine, but it was largely ignored. Named phenylisopropylamine because the starting compound was phenyl-2-propanone (P2P) rather than plant derived ephedrine. This is because amphetamine is weaker when made from the precursor ephedrine than from P2P
- In the 1920s, there was a shortage of ephedrine due to a civil war in China, as a result, in 1927, the allergist, Gordon Alles, resynthesized amphetamine.
- In 1933, pharmaceutical company Smith, Kline & French released amphetamine in an inhaler under the trade name Benzedrine, as a decongestant for blocked nose & asthma. Studies of Benzedrine followed whereupon its mood enhancing & energising properties became increasingly apparent.
- Benzedrine & amphetamine tablets were widely used in World War II to increase alertness, especially amongst long range bomber pilots. But it became increasingly clear that performance enhancing effects were largely in the mind of the users, whereas objectively, their performance was impaired, despite an elevation in mood. This combined with the addictive properties led amphetamine to be used less as the war continued.
- During the Hippie era in the 1960s, there was an epidemic of amphetamine use. This gave rise to moral panic, raising the problem of drug addiction generally up the political agenda. Nenzedrine inhalers were banned and the regulation of prescription amphetamine came into force in both the US and the UK at the end of that era (1970s)

METHAMPHETAMINE

- **Nagayoshi** extracted ephedrine from ephedra plant in **1885**. His further research into chemical manipulation of ephedrine led to the creation of meth (powdered form).
- Development of the crystalline form of methamphetamine was developed by **Akira Ogata** in **1919**. Methamphetamine is simpler to produce compared to amphetamine. It has a similar chemical structure to amphetamine with the addition of a methyl group which allows it to be more easily absorbed into the CNS.
- **1939-1945:**
 - during WWII Germany manufactured & distributed more than 35 million tablets of meth which contributed to the rapid invasion of Europe AKA Blitzkrieg or “lightning war”, but they halted production during 1941 following recognition of its dangerous potential.
 - Japanese provided meth throughout the war, particularly to Kamikaze pilots
 - Civilian meth abuse multiplied by the end of the war when military supplies were opened for sale to the Japanese public.

OTHER: These drugs have mixed/combined effects on the CNS

MDMA (3,4-methylenedioxy-N-methylamphetamine) is classified by the NSW Health as substance in the “Other”. MDMA is classified as both a stimulant and a hallucinogen.

- Often classed within the ‘amphetamine’ group in some classification systems thus, it has a Stimulant classification. However, it has a greater empathogenic effect than general stimulants (increased empathy or love of others, thus street name “Ecstasy”). It is also classified as a Hallucinogen- Different experiences across individuals (hence “Other” classification)
- Primary precursor is Safrole, a light oily liquid extracted from the root-bark or the fruit of the sassafras tree. There are numerous published methods for synthesising safrole into MDMA.
- It was first synthesised in **1912** by the German chemist **Anton Köllisch** who worked for the pharmaceutical company called Merck. The aim for Köllisch was to develop a haemostatic substance to stop abnormal bleeding.
- Following synthesis in 1912 it lay dormant in Merck’s library for 65 years. Its development into a street drug followed this timeline:
- **1927:** Merck scientist Max Oberlin reports MDMA’s similarity to ephedrine (precursor of meth/amphetamine).
- **1953:** US military commissions studies with a range of psychoactive compounds including MDMA (declassified in 1973).
- **1958:** independent synthesis of the same compound in Japan by Yutaka Kasuya.
- **1970:** First report of recreational MDMA use in the US.
- **1970s:** Pharmacist Alexander Shulgin synthesizes MDMA publishes reports of its mood enhancing effects & improvement of therapeutic engagement.
- **1980s:** MDMA becomes increasingly popular in dance/rave culture.
- **1985s:** State prohibition of the compound is introduced.
- **2010s:** MDMA usage decreasing due to scarcity of precursor chemical (safrole) due to substitution by so called ‘designer’ drugs (e.g. mephedrone, BZP, MDPV, methylone) which have been rediscovered by illicit drug chemists from archaic academic documents to sidestep prohibitive laws against of existing drugs.

CANNABIS plant is believed to have originated in the mountainous regions northwest of the Himalayas.

- Two key varieties:
 - Sativa: greater fibre content and therefore, useful for making woven material and has a higher psychotomimetic effect.
 - Indica: has a lower fibre content and therefore, low psychotomimetic effect
- It is thought that these two varieties were separated from the wild type (which has intermediate properties) through selective breeding imposed by earlier generations of the native population who made use of the plants for intoxication, clothes, nets, rope and string

- Direct evidence for the earliest cannabis consumption for drug/ritual effect comes from a preserved burial site in Turpan, North-West China dating around **Circa 1000BC**.



- The 'shaman' has on his person 789g of cannabis.
- This site is especially important because it is the earliest recorded site in which researchers were able to conclusively demonstrate the presence of THC (the psychoactive component of cannabis)
- Earlier ancient texts refer to the medicinal/intoxicant/spiritual effects of cannabis:
 - 2700BC: Chinese herbal medicine the Pênts'ao Ching
 - 2000BC: religious/philosophical text the Hindu Vedas.
 - Later references to cannabis in Japanese, West Asian, Middle Eastern, North African, Roman & Germanic texts chart the spread of cannabis use across the ancient world following the trade routes of the steppe highway/silk road - the chain of exchange that then linked the east and west.

Country	Cultivated (ha)	Eradicated (ha)	Harvestable (ha)	Production (tons)		Plants eradicated		Sites eradicated	
				Indoor	Outdoors	Indoors	Outdoors	Indoors	Outdoors
Afghanistan	10,000				1,400				
Albania					50		33,000		154
Australia						17,668	35,146	322	240
Azerbaijan	6	6	0		308		7,538		121
Bosnia and Herzegovina							2,807		3
Brazil		22			185		616,133		5
Bulgaria						6,913		42	
Chile						18,526	216,902	1,377	291
Costa Rica	8	8	0				965,320		129
Italy						7,706	4,114,911	458	1,318
Latvia						3,796	101	4	3
Lebanon	3,500	800	2,700						
Mexico		9,058			12,166				
Morocco	52,000	5,000	47,000	760	38,000				
New Zealand						21,202	119,059	783	
Philippines		21					1,224,738		188
Poland		4					58,156	687	627
Tajikistan							2,180,121		
Ukraine	529						2,200,000		
United States of America						302,377	3,631,582	2,596	6,470

UNODC, World Drug Report (2014)- contemporary cultivation of cannabis is global

- Cannabinoids are the main psychoactive component within the cannabis leaf. There are two forms:
 - Phytocannabinoids: found in plants
 - Synthetic cannabinoids: man made from other compounds.
- Around 85 phytocannabinoids have been isolated from the cannabis plant
- most research has focused on Δ^9 -tetrahydrocannabinol (THC) & cannabidiol (CBD).
- THC: primary psychoactive intoxicant, as indicated by the fact THC dose consumed is associated with the subjectively reported drug effect
- The supposed potency of different forms of the drug have different THC concentrations:
 - Cannabis herb (leaves) 5%
 - Flowers (buds) 12%

- Resin (Hashish) 20%
- Oils (Hash oil) 60%
- There is initial evidence that although CBD has little psychoactive effect it may reduce the psychotomimetic effect of THC
- The implication that the psychoactive effect of cannabinoids can be isolated to THC has been crucial in justifying the use of cannabinoids as medicines for a variety of ailments. Medical marijuana is higher in CBD and lower in THC so that CBD can counteract the psychoactive effects of THC.
- There is now sufficient evidence for the efficacy of cannabinoids as treatments for them to return to mainstream biomedical research

Overview of controlled trials of cannabis medications for established indications*¹

Indication	Number of randomized controlled trials (some three-armed)	Positive studies	Negative studies
Spasticity	n = 12 (dronabinol: [e1, e2, e4–e6]; cannabis: [e1–e3, e6–e12]) in multiple sclerosis	n = 9 (e4–e12)	n = 3 (e1–e3)
	n = 3 (dronabinol: [e13–e14]; nabilone: [e15] in paraplegia)	n = 3 (e13–e15)	–
Nausea and vomiting due to cytostatics	n = 41 (dronabinol: [e16–e34]; cannabis cigarettes: [e25]; cannabis extract: [e35]; nabilone: [e36–e52]; levonantradol: [e53–e56])	n = 40	n = 1 (e18)
Loss of appetite/weight loss	n = 7 (dronabinol: [e59–e65]; cannabis cigarettes: [e63–e65]) in HIV/Aids	n = 7	–
	n = 4 (dronabinol: [e66–e68]; cannabis extract: [e69]) in various tumor diseases	n = 3	n = 1 (e69)
	n = 1 (dronabinol: [e70]) in Alzheimer's disease	n = 1	–
Chronic pain	n = 14 (dronabinol: [e71–e74]; nabilone: [e75, e76]; cannabis extract: [e73, e74, e77–e79]; cannabis cigarettes: [e80–e83]; CT3 (ajulemic acid): [e84]) in neuropathic pain or pain in MS	n = 12 (e71, e73–e75, e77–e84)	n = 2 (e72, e76)
	n = 12 (dronabinol: [e85–e87, e93]; NIB: [e88]; benzopyrano-peridine: [e89]; cannabis extract: [e87, e90, e94]; nabilone: [e91, e92, e96]; cannabis cigarettes: [e95]) in chronic pain (cancer, rheumatism, fibromyalgia)	n = 11 ([e85, e86, e87] cannabis extract, [e88, e90–e96])	n = 2 ([e87] dronabinol, [e89])

- A number of synthetic cannabinoids have been created:
 - **John William Huffman**, a Professor of organic chemistry synthesised a whole series (JWH-018) his work was funded by the National Institute on Drug Abuse (NIDA)
 - **Professor Raphael Missoula**, Hebrew University developed HU-210
 - **Pfizer** developed CP 47,497
 - There are many more...
- These synthetic cannabinoids are considered designer drugs, so called 'spice' products mixed herbs infused with synthetic cannabinoids

One might marvel at the speed and accuracy with which the complex experimental procedures required to make these compounds were recreated by illicit drug chemists. But then again, leaders of the drug trade must surely be aware that meth/amphetamine, heroin, MDMA & cocaine all began as academic experiments before becoming global billion dollar industries.
