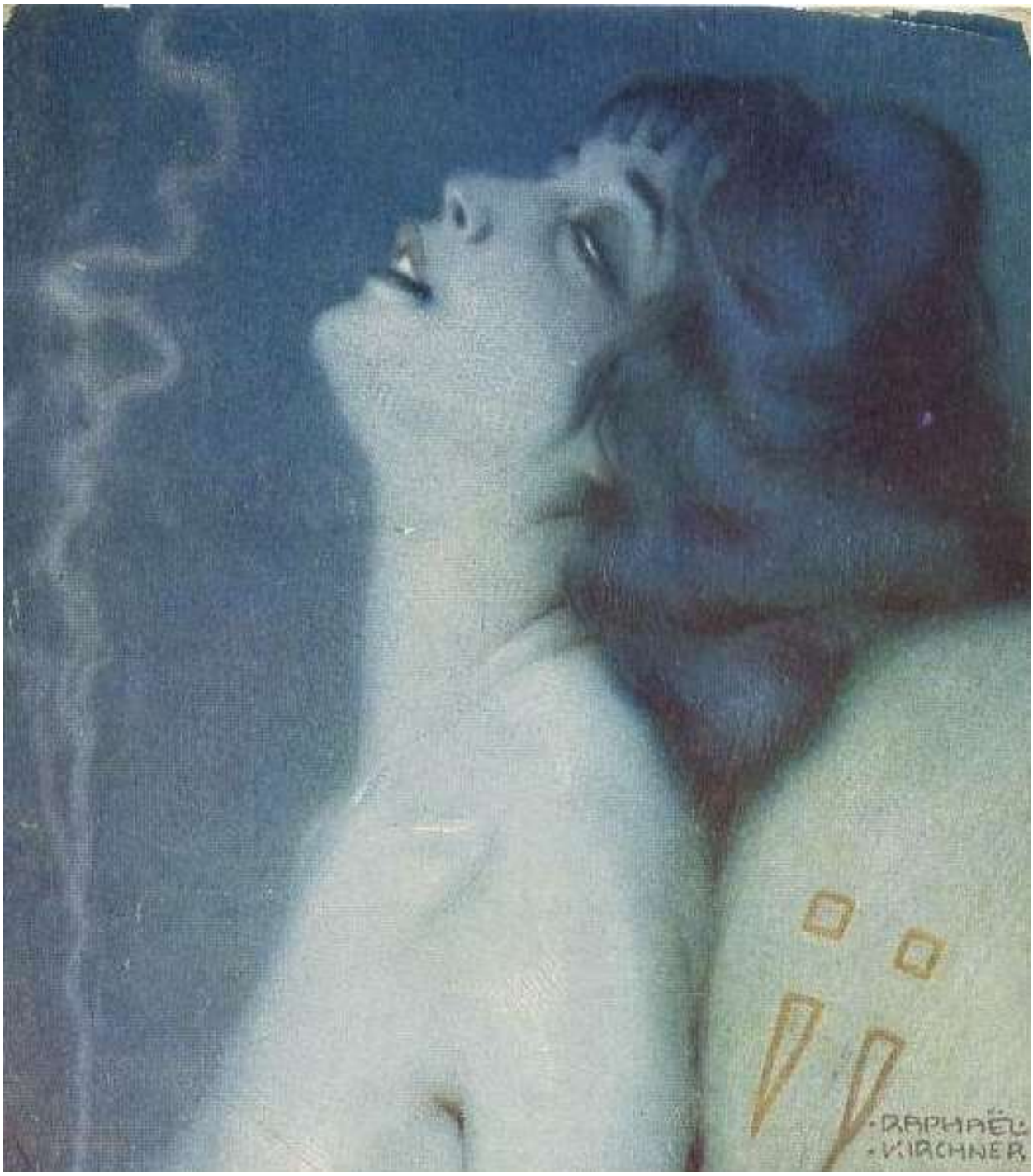
THE NORTHERN HOSPITAL

CANNABIS SYNTHETIC ANALOGUES



"Lélie, fumeuse d'opium", Raphael Kirchner postcard, 1911.

Kirchner's wife was the model for many of his images. She was an habitual opium smoker, a habit considered the height of decadent chic among the Parisian Avant garde at the turn of the 20th Century. With the proliferation of a vast array of new synthetic cannabinoids, Ms Kirchner would have been right at home in the early 21st Century!

At first, a certain absurd, irresistible hilarity overcomes you.

The most ordinary words, the simplest ideas assume a new and bizarre aspect.

This mirth is intolerable to you; but it is useless to resist. The demon has invaded you...

It sometimes happens that people completely unsuited for word-play will improvise an endless string of puns and wholly improbable idea relationships fit to outdo the ablest masters of this preposterous craft.

But after a few minutes, the relation between ideas becomes so vague, and the thread of your thoughts grows so tenuous, that only your cohorts... can understand you.

Next your senses become extraordinarily keen and acute. Your sight is infinite.

Your ear can discern the slightest perceptible sound, even through the shrillest of noises.

The slightest ambiguities, the most inexplicable transpositions of ideas take place. In sounds there is color; in colors there is a music...

You are sitting and smoking; you believe that you are sitting in your pipe, and that your pipe is smoking you; you are exhaling yourself in bluish clouds.

This fantasy goes on for an eternity. A lucid interval, and a great expenditure of effort, permit you to look at the clock. The eternity turns out to have been only a minute.

The third phase... is something beyond description. It is what the Orientals call kef; it is complete happiness.

There is nothing whirling and tumultuous about it. It is a calm and placid beatitude. Every philosophical problem is resolved.

Every difficult question that presents a point of contention for theologians, and brings despair to thoughtful men, becomes clear and transparent.

Every contradiction is reconciled.

Man has surpassed the gods.

Charles Baudelaire, "Les Paradis Artificiels", (Artificial Paradises), 1860

In "Artificial Paradises", Charles Baudelaire explored the state of being under the influence of opium and hashish. His work was partly inspired by Thomas de Quincey's "Confessions of an English Opium-Eater". He explored the motivations of the addict, as well as the bizarre psychedelic experiences that they could have. He foreshadowed much later similar work that would emerge in the 1960s particularly in regard to the effects of LSD. Today modern clandestine chemistry is producing ever increasing numbers of artificial psychedelic drugs, such as the synthetic cannabinoids.

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Introduction

There has been a recent proliferation of illicit (and many currently legal) unregulated **psychoactive** substances, freely available from internet sources and some other retail outlets.

The majority of these new drugs can be characterized as:

- Synthetic cannabinoids
- Amphetamine-like stimulants
- Opioid-like substances
- Hallucinogens

The following refers to the **synthetic cannabinoids** or **Synthetic Cannabinoid Receptor Agonists (or SCRAs)**

No less than **170** individual synthetic cannabinoid receptor agonists have been detected in the EU to date. [3]

Many of these agents possess considerable toxic profiles including lethality

Rigorous study of SCRAs is extremely difficult, as the variety of herbs and synthetic cannabinoids create a moving target and so most remain unfamiliar to health care providers.

SCRAs continue to evolve over time, aiming to evade legislative control.

Effects can be unpredictable because of the large array of agents being produced

Terminology:

A great variety of "street" name terminology has proliferated around the synthetic cannabinoids including:

- Marley
- Black Widow
- Genie
- K2
- K9
- Yucatan Fire
- Spice
- Spice Gold
- Spice Silver
- Kronic
- Spice Diamond
- Halo
- Ash
- Spice
- Summit
- Inferno
- Damiana
- Drolle

- Exodus and Blue Exodus - are thought to contain synthetic cannabinoid receptor agonists

History

Research into the neurobiology of the cannabinoids led to the discovery of an endogenous "cannabinoid system".

The first of the cannabinoid receptors - CB-1- was identified in 1990 and this finding revolutionized the study of cannabinoid biology. Since then, a multitude of roles for the endogenous cannabinoid system has been proposed.

Sources

The synthetic cannabinoid receptor agonists are usually sprayed onto a "herbal mixture/ blend" of dried plant material.

The material is then usually smoked.

Exact ingredients of any one substance can vary greatly, especially as legislation changes. Different products will have different compositions. Sold in blends that often contain more than ten herbal additives, the substrate herbs are currently difficult or impossible to identify.

The substances are usually sold via the internet or "head shops", (i.e. a retail outlet specializing in tobacco paraphernalia). They may also be sold as "incense" and marked "not for human consumption".

Information on product packaging will often not list synthetic cannabinoid receptor agonists but will often list "herbal ingredients" in various ways in order to circumvent legislation.

Biochemistry

A large number of endogenous cannabinoid neurotransmitters or endocannabinoids have been identified, and CB-1 and CB-2 cannabinoid receptors have been characterized. The CB-1 receptors exert a neuromodulatory role in the central nervous system and enteric plexus. Cannabinoid type 2 receptors have an immunomodulatory effect and are located on tissues such as microglia.

Synthetic cannabinoid agonists can be divided into seven major structural groups: [5]

1. Naphthoylindoles (JWH-018 and JWH- 073)

2. Naphthylmethylindoles

3. Naphthoylpyrroles

4. Naphthylmethylindenes

5. Phenylacetylindoles (JWH-250)

6. Cyclohexylphenols (CP47,497)

7. Classical cannabinoids (HU-210)

Toxicology

Synthetic cannabinoid receptor agonists (SCRA) are full **CB1** and **CB2** receptor agonists with a **higher potency** than delta-9-trans-tetrahydrocannabinol found in natural cannabis.

The psychoactivity of the SCRAs is associated with their **CB1** receptor affinities

Pharmacokinetics

There is essentially no human evidence that describes the absorption, distribution, metabolism, or elimination of the synthetic cannabinoids.

In general terms:

Absorption:

- Most of these agents will be smoked / occasionally they are ingested or injected.

  More recently they are also being sold as an "e-liquid" (i.e. for "electronic" or **e - cigarettes**).

Distribution:

- Cannabinoids in general are extremely lipophilic and bind avidly to cerebral fat.

Metabolism and excretion:

- Cannabinoids in general have long half-lives.

- Regular use is cumulative and this might give rise to toxicity in the sensitive patient

Risk Assessment

Synthetic cannabinoid receptor agonists generally have a higher affinity for the cannabinoid CB_1 receptor than delta 9-THC (found in cannabis) and, therefore, are significantly more potent.

The exact risk is difficult to assess however due to the vast array of current agents and new agents becoming available.

Exact chemical compositions, doses and impurities are unknown and so effects can be unpredictable

The risk profile for **natural cannabis** includes the following points:

- Effects are synergistic with other CNS depressant drugs.

- Chronic use leads to neuropsychiatric sequelae.
- **Ingestion in children can lead to prolonged and life threatening coma.** [1]
- Chronic heavy users can develop a physical dependence with a withdrawal syndrome when usage stops.

Clinical Features

The onset of effects occur within **1-2 hours**

Cannabinoid toxicity:

The general features of cannabinoids **as a class** are as follows:

1. CNS:

   Central:

   - Euphoria/ dysphoria.
     - ♥ Including anxiety/ paranoia/ panic attacks.
   - Slurred speech.
   - Depersonalization.
   - Impaired cognitive function.
   - Impaired perception:
     - ♥ The effects of marijuana on perception and coordination are responsible for serious impairments in driving abilities.
   - Acute psychosis, (higher doses):
     - ♥ Including frank **delusions** and **hallucinations**
   - Sedation:
     - ♥ Sedation/ prolonged coma may occur in **children** for up **36 hours.**
     - ♥ Sedation is common in adults, but *profound* coma is not seen in adults.
   - Alteration of seizure threshold:

     This is an area of uncertainty and controversy.

Overall it may be that cannabis has some **mild anticonvulsant** effects.

The marijuana plant itself contains over *100 organic compounds*, and the various compounds have different effects so it is difficult to determine which actual compound has what effect.

Peripheral:

- Incoordination which may be indicated by a positive Romberg test or ataxia and loss of fine motor coordination.

2. CVS:

- Tachycardia / hypertension.
- Orthostatic hypotension.

3. GIT:

- Acute GIT upset with nausea, abdominal cramps and diarrhea.

4. Ocular:

- **Conjunctival hyperemia**, which may be marked, is a common sign.
- Possible dose-related mydriasis of the pupils.

5. Respiratory:

Rarely, in inhalation:

- Pneumothorax
- Pneumomediastinum

Additional toxicity of Synthetic Cannabinoids:

A vast array of additional toxic effects are seen in addition to the "traditional" toxic profile of natural cannabis - reflecting the varied chemical nature, combinations and impurities of any given agent.

Among the more important adverse effects that have been reported are:

1. **Seizures**
2. **Electrolyte disturbances - hypokalemia in particular.**
3. **Myocardial Toxicity.**
4. **Acute kidney injury.**

5. **Rhabdomyolysis**

Investigations

Investigation may be required to rule out alternative diagnoses or secondary complications.

1. Blood tests:

   - FBE
   - U&Es/ glucose
   - CK/ myoglobin (rhabdomyolysis suspected).

   Others as clinically indicated.

2. 12 lead ECG:

   - ACS
   - QT prolongation
   - Consider cardiotoxic coingestion.

3. Blood and Urine cannabinoid screens:

   - **Most synthetic cannabinoid receptor agonists do *not* give a positive result on current routine urine toxicological screening for delta-9-tetrahydrocannabinol (THC).** [3]

4. Consider coingestion of alcohol/ paracetamol

Management

Management is supportive

1. Immediate attention to ABC issues as required.

2. Acute agitation/ psychosis:

   - Mild symptoms may be treated with oral diazepam.
   - Sedation with IM or IV benzodiazepines may occasionally be required for more severe symptoms.
   - For severe agitated delirium:
     - ♥ Droperidol 10 mg IM / 2.5-10 mg IV initially.

3. Seizures:

- Treat along usual lines with IM - IV benzodiazepines.

4. Antiemetics are given for nausea / vomiting

   Options include:

- Prochlorperazine
- Metoclopramide
- Ondansetron/ granisetron
- Droperidol (for more intractable cases)

5. Hypotension:

- This will usually respond well to IV fluid resuscitation.

6. **Anticipate unexpected effects:**

- **As the exact chemical natures of the many newer synthetic cannabinoids are unknown, symptoms and signs not typical of pure cannabis intoxication may be seen**

Disposition:

For patients who have taken "cannabis" advice should be sought from a toxicologist when symptoms and signs are atypical.

The majority of patients will recover **within 6 hours** after a period of observation

References

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