JWH-250

Critical Review Report

Agenda item 4.11

Expert Committee on Drug Dependence

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Acknowledgments

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Contents

Summary

JWH-250 is a synthetic cannabinoid receptor agonist (SCRA) with a potency comparable to that of delta-9-tetrahydrocannabinol (THC). JWH-250 has affinity for CB_1 and CB_2 receptors, and shows three-fold selectivity for CB_1-receptors.

JWH-250 is a psychoactive substance and has effects similar to those of THC. It has been detected in herbal products marketed under a variety of names via the Internet and in specialised shops. The quantity of JWH-250 among the different packages may vary considerably.

No detailed data is available about the toxicity following the consumption of JWH-250 alone, but four cases have been described following overdosing of the compound in combination with other SCRA(s). In these cases, the serum level of JWH-250 was 0.10 ng/ml to 0.40 ng/ml, and the Poisoning Severity Score (PSS) was 1 to 2 (at 6 to 24 hours after consumption). The most frequently observed symptoms in this study (those for JWH-250 were not separately specified) were tachycardia, hypertension, agitation, hallucinations, minor elevation of blood glucose, hypokalemia and vomiting. Chest pain, seizures, myoclonia and acute psychosis were also noted. No data are available about its dependence or abuse potential of JWH-250. Considering its close pharmacological resemblance to THC, abuse of JWH-250 is likely to occur.

1. Substance identification

A. International Nonproprietary Name (INN)

Not applicable.

B. Chemical Abstract Service (CAS) Registry Number

864445-43-2

C. Other Names

1-pentyl-3-(2-methoxyphenylacetyl)indole
1-(1-pentyl-1H-indol-3-yl)-2-(2-methoxyphenyl)ethanone
JWH-250

D. Trade Names

No information available.

E. Street Names

No information available.

F. Physical properties

In pure form, JWH-250 is a white powder.

G. WHO Review History

JWH-250 was not previously pre reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that JWH-250 is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

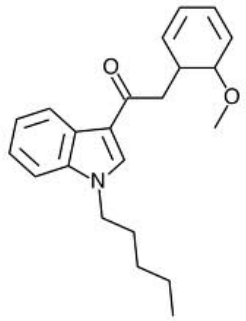
2. Chemistry

A. Chemical Name

IUPAC Name: 2-(2-methoxyphenyl)-1-(1-pentylindol-3-yl)ethanone
CA Index Name: 2-(2-methoxyphenyl)-1-(1-pentylindol-3-yl)ethanone

B. Chemical Structure

Free base:



JWH-250

Molecular Formula: C22H25NO2
Molecular Weight: 335.2
Melting point: 82.6 °C
Boiling point: -
Fusion point: -

C. Stereoisomers

No stereoisomers exist.

D. Synthesis

JWH-250 was synthesized from 1-pentylindole and 2-methoxyphenylacetylchloride by the Okauchi modification of the Friedel-Crafts reaction.[11]

E. Chemical description

JWH-250 belongs to the category of the phenylacetylindoles and has structural resemblance to other synthetic cannabinoids with a core indole structure, such as the Schedule I substances JWH-018 and AM2201.

F. Chemical properties

No particular properties.

G. Chemical identification

NMR, FTIR and chromatographic methods with mass spectrometric detection are available for the identification of JWH-250.[5;21]

3. Ease of convertibility into controlled substances

Based on its structure, it is not likely that JWH-250 can be converted into a controlled substance.

4. General pharmacology

4.1. Pharmacodynamics

JWH-250 belongs to the category of the synthetic cannabinoid receptor agonists (SCRAs). SCRAs mimic the effects of delta-9-tetrahydrocannabinol (THC) by binding to the CB_1 and CB_2 cannabinoid receptors in the brain and peripheral organs.

In the early 1990s, two cannabinoid receptors have been identified and named CB_1 and CB_2. CB_1 is primarily localised in the central nervous system (CNS), and CB_2 in cells mainly associated with the immune system, such as macrophages, lymph nodes, spleen, and microglia cells.[8;16;18;27] CB_1 receptors are mainly found in the CNS-regions involved in cognition, short-term memory, movement and motor function.[3] Activation of the CB_1 receptor by THC or SCRAs modulates amongst others neurotransmitter release in many inhibitory and excitatory synapses in the brain. These effects are mediated through CB_1 receptor coupled G-protein activation and finally result in decreased activity of cAMP-dependent protein kinases.

For the cannabimimetics commonly found in herbal products, only few data in terms of their potency are available.[29] Wiley *et al.*, (2013) reported receptor binding data (CB_1 and CB_2) and in vivo potencies (spontaneous activity, anti-nociceptive effect, rectal temperature, and ring immobility) of almost forty different JWH-compounds, but JWH-250 was not included.[31] Previously, the binding of JWH-250 was reported by Huffman et al[11] (cf. Table 1).

Using a molecular model of CB_1 and CB_2 cannabinoid receptors, the interaction i.e. binding affinity of some 120 different SCRAs with both receptors was estimated taking into account the transition from the inactive conformation of the receptor (R) to the active (R*) one.[24] Their calculations showed that JWH-250 was one of the nine ligands with the highest affinity to the CB_2-receptor. All those nine ligands contained an ortho substituent on the aryl ring.

Table 1. Binding affinity of JWH-250 and THC (mean ± SEM) to CB_1 and CB_2 receptors.[11]

Compound	Ki CB_1 (nM)a	Ki CB_2 (nM)a	Ratio	Method	Reference
JWH-250	11 ± 2	33 ± 2	0.33	a	11
THC	40.7	36.4			2
THC	15.3	25.1			17
THC	67	36	1.86	a	30

a CB_1: displacement of CP-55,940 at rat brain membranes; CB_2: cloned human receptor preparation; ratio: K_i CB_1 / K_i CB_2

4.2. Routes of administration and dosage

As a substitute for cannabis, JWH-250 is usually smoked or sometimes ingested. The dose required for the desired effect(s) is unknown.

4.3. Pharmacokinetics

Analysis of urine of rats treated with JWH-250 or of suspected users showed the following metabolites: (a) trihydroxylation combined with dehydration of the N-alkyl chain, (b) mono- and dihydroxylation of aromatic and aliphatic residues of JWH-250, (c) N-dealkylation and (d) N-dealkylation and monohydroxylation. While N-dealkylated and N-dealkyl monohydroxylated forms were found in rats, the prevailing urinary metabolites in humans were the monohydroxylated forms.[9]

5. Toxicology

No pre-clinical safety data are available about the toxicity, reproductive impact and mutagenic/carcinogenic potential of JWH-250.

6. Adverse reactions in humans

Papanti *et al.*, (2013) reviewed 223 studies (only four referred to JWH-250) about SCRA-related psychopathological symptoms that included appropriate toxicological confirmation. The studies suggested that psychotic symptoms such as hallucinations and delusions may occur in acute/chronic SCRA users.[19]

Between September 2008 and February 2011, 29 cases of acute intoxication after smoking a herbal product were reported by Hermanns-Clausen et al.[10] In four of these cases, JWH-250 was found in serum together with other SCRAs (cf. Table 2).

Table 2. Serum concentrations (ng/ml) of JWH-250 and other SCRAs identified in four cases[10]; Poisoning Severity Score[20] (PSS) and length of symptoms were reported by Kneisel.[12]

Case no.	JWH-250	JWH-018	JWH-081	JWH-122	PSS	Symptoms
1	0.33	0.40	4.0	-	2	24 hrs
2	0.10	-	-	0.17	1	14 hrs
3	1.1	-	3.0	-	1	6 hrs
4	0.26	< 0.10	-	40	2	12 hrs

In these four cases, the serum concentrations of JWH-250 were low (0.1-1.1 ng/ml), suggesting that the observed clinical symptoms were rather due to SCRAs other than JWH-250. The most frequently observed symptoms in this study (those for JWH-250 were not separately specified) were tachycardia, hypertension, agitation, hallucinations, minor elevation of blood glucose, hypokalemia and vomiting. Chest pain, seizures, myoclonia and acute psychosis were also noted.

From January 2010 to December 2011, 32 cases of acute poisoning were recorded in an Italian study.[15] The consumption of SCRAs was confirmed by toxicological analysis in 19 cases of which the combination of JWH-250 with JWH-122 was found in three cases. Patients aged 14-21 years were overrepresented (62.5%; mean age 23.5 years). Clinical symptoms most frequently observed were tachycardia (21/32), agitation (16/32), confusion (13/32), mydriasis (12/32), hallucinations (6/32), coma

(4/32) and convulsions (2/32). All patients were treated symptomatically and in most cases discharged after 24-36 hours.

During 2008–2010, the Pavia Poison Centre (Italy) identified 17 cases of SCRA overdosing (age range 14–55 years). The main clinical symptoms were tachycardia (13), agitation/anxiety (12), confusion (8), mydriasis (7), hallucinations (5), and paraesthesia (5). In 11 out of the 17 cases, SCRAs were detected in the blood: JWH-122 (5 cases), JWH-122 (3 cases) and JWH-250 (3 cases), JWH-018 (2 cases). Patients received symptomatic treatment and were discharged symptom-free within 24 hours after exposure.[14]

Using telephone inquiries (2007 until the end of October 2010), Westenbergh and Hulten[28] collected data about 214 SCRA cases of overdosing in Sweden. Cases mainly referred to young adolescent males (42% were under 20 years old; 78% males). Clinical symptoms were mild (74% with Poison Severity Score of 1) or moderate (26% with Poison Severity Score of 2), while no severe or lethal cases were noted. Clinical symptoms commonly reported were tachycardia (51%), drowsiness (36%), mydriasis (28%), muscular symptoms (26%), hypertension (13%) and vomiting (12%). Most patients experienced typical symptoms but a few presented atypical symptoms, e.g., unconsciousness, loss of eyesight and speech. In 56 (26.2%) cases, 26 SCRAs were identified in the herbal mixture consumed of which JWH-081 and JWH-250 appeared the most frequent. In only 22 cases (10%), serum samples were available for analysis. Fourteen serum samples were positive for one or two synthetic cannabinoids: JWH-018 (2 cases), JWH-081 (11 cases), JWH-250 (2 cases) and JWH-015 (3 cases).

Kronstrand *et al.,* (2013) presented eight cases of overdosing with SCRAs between begin of 2011 and early 2013 where blood from subjects suspected of an innocent drug offence or driving under the influence of drugs (DUI) was analysed.[13] Of 3,078 blood samples analysed, 28% were found positive for one or more SCRAs. JWH-250 (N = 3) had mean (median) concentrations of 0.42 ng/ml (0.40 ng/ml).

In an experimental study, volunteer I smoked an incense product (Legal Eagle), containing JWH-250, JWH-019, JWH-081, RCS-4 (~10 mg/g), whereas volunteer II smoked 8-Ball, containing JWH-081 and JWH-250 (~10 mg/g). Peak blood levels of volunteer I at 20 min post dosing were 50 ng/ml for JWH-081, 38 ng/ml for JWH-019, 10 ng/ml for JWH-250, and 10 ng/ml for RCS-8. Peak blood levels of volunteer II at 20 min post dosing were 16 ng/ml for JWH-081 and 7 ng/ml for JWH-250. The following clinical symptoms were observed: agitation, paranoia, psychomotor restlessness, unsteady gait, loss of balance, perceptual disturbances.[1]

A 19-year-old male had two witnessed generalized convulsions soon after smoking a Spice product “Happy Tiger Incense”. The man was healthy, i.e., he had never experienced convulsions before nor was he on any medication. Paramedics found a slightly confused patient and during transport to the hospital the patient vomited and had a second generalized convulsion, which was treated with midazolam. The urine was positive for benzodiazepines, and negative for amphetamines, barbiturates, opiates, and benzoylecgonine (cocaine metabolite). Four synthetic cannabinoids (JWH-018, JWH-081, JWH-250, and AM-2201) were identified in the remains of the product smoked, but quantitative analysis was not performed.[23]

In 2010, the US Poison Control Centers received 2,947 of exposure calls for synthetic cannabinoids. Synthetic cannabinoids were identified in 32 States. Nearly two-thirds were identified as JWH-018 (1887 reports; 63%), whereas JWH-250 was reported 418 times (14%).[4] Up to 2012, UN Member States identified to UNODC JWH-018 (70 reports) as the most widespread synthetic cannabinoid, followed by JWH-073 (57 reports) and JWH-250 (37 reports), all of which are aminoalkylindoles.[25]

In summary, it is not possible to draw conclusions about the toxicity of JWH-250 in humans, because no toxicity data are available following overdosing of JWH-250 alone, i.e., only the toxicity has been described following the consumption of JWH-250 in combination with other SCRAs.

7. Dependence potential

No study data on the dependence potential of JWH-250 is available.

8. Abuse potential

No study data on the abuse potential of JWH-250 is available.

Considering the close pharmacological resemblance between JWH-250 and THC, abuse of JWH-250 is likely to occur.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

JWH-250 does not have any therapeutic application.

10. Listing on the WHO Model List of Essential Medicines

Not listed.

11. Marketing authorizations (as a medicine)

JWH-250 is not marketed as a medicine.

12. Industrial use

No data available.

13. Non-medical use, abuse and dependence

JWH-250 has been encountered as adulterants in numerous herbal products that are smoked for their psychoactive effects. However, the extent of the use of these products (either or not containing JWH-250) is largely unknown.[7]

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

The general view is that JWH-250, like other SCRAs, is used as a substitute for cannabis. In general, adverse effects of SCRA intoxications are more intense than with cannabis, possibly because of their high activity and ease of overdosing.[7] There appears to be a wide variety of herbal products containing a variety and varying quantities of SCRAs.[7]

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

15. Licit production, consumption and international trade

No commercial or medical uses are known.

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

16. Illicit manufacture and traffic and related information

No data about the manufacture is available.

JWH-250 was identified in "Spice" products in Germany.[6] In May 2009, the German Federal Criminal Police identified JWH-250 as a new ingredient in herbal smoking mixtures for the first time. Since then, JWH-250 has been detected in 'Euphoric Blends White Rhino', 'Euphoric Blends Big Bang', 'Euphoric Blends Bubble Gum', 'Electric Puha Ganja Guru Delta', 'Kronic Skunk', 'Space V2 Herbal Incense' and 'Spice Diamond'.[22] In 420 out of over 2000 samples seized in Polish head shops and from individuals during 3.5-years (2008-2011), JWH-250 was detected 75 times. Common dual combinations were JWH-073 + JWH-250 (16 products) and JWH-081 + JWH-250 (12 products).[32]

The global emergence retrieved from the UNODC Early Warning Advisory on NPS is listed in Table 3.[26]

Table 3. Global emergence of JWH-250.[26]

List of countries (21)	
Australia	Netherlands
Bulgaria	New Zealand
Canada	Norway
Croatia	Portugal
Finland	Romania
Greece	Russian Federation
Hungary	Spain
Israel	Turkey
Italy	United Kingdom
Latvia	United States
Lithuania	

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

17. Current international controls and their impact

JWH-250 is currently not under international control.

18. Current and past national controls

JWH-250 is under national control in several countries including the USA, Germany, Luxembourg, Italy, Czech Republic, Latvia, and Sweden.

Please refer Annex 1: Report on WHO questionnaire for review of psychoactive substances.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

No remarks.

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Annex 1:
Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation of JWH-250

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 64 Member States answered the questionnaire for JWH-250. Of these, only 31 respondents (AFR 1, AMR 5, EUR 22, WPR 3) had information on this substance.

LEGITIMATE USE

None reported that JWH-250 was currently authorized or is in the process of being authorized/registered as a medical product in their country. Seven respondents stated that this substance was used in research or as reference analytical standards. There was no use stated for animal/veterinary care

HARMFUL USE

Twenty-two respondents confirmed that there was recreational/harmful use of JWH-250; the common routes of administration were stated as, inhaling/sniffing by 14, and 2 each oral/inhaling/sniffing, oral/injection/inhaling/sniffing and oral. Sixteen respondents stated this was obtained only via trafficking, 3 via trafficking plus clandestine manufacturing and 1 each via clandestine manufacturing and diversion plus trafficking. Fourteen respondents reported on the common formulations available with 11 reporting powder, 2 liquid and 1 powder/liquid forms. Two respondents also mention that JWH-250 is often smoked and 5 that it is often found in herbal mixtures. When asked if JWH-250 was used by any special populations 6 stated only general population, 3 only clubs and 1 general population and clubs. Four respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by JWH-250. These include vomiting, loss of consciousness, , mydriasis, hallucinations, nausea, vision disorders, tachycardia, anxiety, agitation, irritability, seizures, hypokaliemia, paranoia, panic attack, dyspnoea and psychoses. One respondent reports drug related crime on delivery of NPS.

Additional information provided ‘in 2012, the American Association of Poison Control Centers (AAPCC) has reported receiving an excess of 5,200 exposure calls corresponding to products purportedly laced with synthetic cannabinoids, although the data provided does not generally include biological sample testing that would confirm to which cannabinoid the user was exposed.’

CONTROL

Of those with information on the substance, 28 reported that JWH-250 was controlled under legislation that was intended to regulate its availability; 22 under “controlled substance act”, 5 under “medicines law” and 1 under “other” legislations. Only 3 respondents stated that there were challenges with the implementation of this legislation. On illicit activities involving JWH-250, four respondents reported clandestine manufacture and one the synthesis of the product itself. Nine respondents reported processing into the consumer product, 17 reported trafficking, 3 reported diversion and 10 an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	2012 (number of respondents)
Total number of seizures	3,056 (13)	871 (14)
Total quantity seized (kg)	410.95 (10) some include other cannabinoids	35.91 (11) some include other cannabinoids
Others seized	Wraps; plant and herbal products also reported	Wraps; plant and herbal products also reported

IMPACT OF SCHEDULING

Twenty-six respondents reported that if JWH-250 was placed under international control, they would have the laboratory capacity to identify the substance. There is no reported medical use.