# Cannabis sativa

## Common Names

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Country</th>
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<tbody>
<tr>
<td>Almindelig hamp</td>
<td>Denmark</td>
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<tr>
<td>Asa</td>
<td>Japan</td>
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<tr>
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<td>India</td>
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<tr>
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<tr>
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<td>Da ma ren</td>
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Marihuana  Russia
Marihuana  Serbia
Marihuana  Spain
Marihuana  Ukraine
Marihuana  United States
Marijuana  France
Marijuana  Italy
Marijuana  Mexico
Marijuana  Portugal
Marijuana  Sweden
Mashinin  Japan
Navadna konoplja  Slovenia
Porkanchaa  Thailand
Pot  Denmark
Qinnib  Arabic countries
Riesen hanf  Germany
Seruma erva  Portugal
Taima  Japan
Til  Arabic countries
Vrai chanvre  France
Weed  Guyana
Xian ma  China
Ye ma  China

BOTANICAL DESCRIPTION
Cannabis sativa is an annual herb of the MORACEAE family that grows to 5 m tall. It is usually erect; stems variable, with resinous pubescence, angular, sometimes hollow, especially above the first pairs of true leaves; basal leaves opposite, the upper leaves alternate, stipulate, long petiolate, palmate, with 3–11, rarely single, lanceolate, serrate, acuminate leaflets up to 10 cm long, 1.5 cm broad. Flowers are monoeccious or dioecious, the male in axillary and terminal panicles, apetalous, with five yellowish petals and five poricidal stamens; the female flowers germinate in the axils and terminally, with one single-ovulate ovary. Fruit is brown, shining achene, variously marked or plain, tightly embraces the seed with its fleshy endosperm and curved embryo; late summer to early fall; year-round in tropics. Drug-producing selections grow better and produce more drugs in the tropics; oil- and fiber-producing plants thrive better in the temperate and subtropical areas. The form of the plant and the yield of fiber from it vary according to climate and particular variety. Varieties cultivated for their fibers have long stalks, branch very little, and yield only small quantities of seed. Oil seed varieties are small, mature early, and produce large quantities of seed. Varieties grown for the drugs are small, much branched with smaller dark-green leaves. Between these three main types of plants are numerous varieties that differ from the main one in height, extent of branching, and other characteristics.

ORIGIN AND DISTRIBUTION
Native to Central Asia and long cultivated in Asia, Europe, and China. Now a widespread tropical, temperate, and subarctic cultivar. Cannabis sativa has been cultivated for more than 4500 years for different purposes, such as fiber, oil, or narcotics. The oldest use of hemp is for fiber, and later the seeds were used for culinary purposes. Plants yielding the drug were discovered in India, cultivated for medicinal purposes as early as 900 BC. In medieval times, it was brought to North Africa, where currently it is cultivated exclusively for hashish or kif.

TRADITIONAL MEDICINAL USES
Afghanistan. Hot water extract of the resin is taken orally to induce abortion. China. Hot water extract of the inflorescence is taken orally for wasting diseases, to clear the blood, to cool the temperature, to relieve fluxes, for rheumatism, to discharge pus, and to stupefy and produce hallucinations. The seed is taken orally as an emmenagogue. Decoction of the seed is taken orally as an anodyne, an emmenagogue, a febrifuge, for migraine, and for cancer. It is taken orally as a hallucinogen and externally for rheumatism.

Guatemala. The leaves are used externally to relieve muscular pains.
India. Hot water extract of the dried entire plant is taken orally as a narcotic and to relieve pain of dysmenorrhea\textsuperscript{CS110}. Hot water extract of the dried flower and leaf is taken orally for dyspepsia and gonorrhea and as a nerve stimulant\textsuperscript{CS117}. Hot water extract of the inflorescence of female plants is taken orally as an abortifacient\textsuperscript{CS010}. Hot water extract of the leaf is taken orally to relieve menstrual pain\textsuperscript{CS086}. For cuts, boils, and blisters, leaf paste is applied topically for 4 days\textsuperscript{CS098}. Hot water extract of the bark is taken orally for hydrocele and other inflammation\textsuperscript{CS125}. Extract of the leaves is used as an insect repellant\textsuperscript{CS246}. Hot water extract of the seed is taken orally as an emmenagogue\textsuperscript{CS010}. The powdered seed is taken orally as an aid in conception. One gram of seeds is powdered, then mixed with water, and given to women in the morning before breakfast for 7 days after menstruation. The use of pepper and cane sugar is avoided. Paste of dried leaves is applied over the anus in the morning and evening for piles\textsuperscript{CS099}. The dried leaf juice is used externally for burns. The oil is extracted by roasting the seeds\textsuperscript{CS213}. Seeds are taken orally for diabetes, hysteria, and sleeplessness\textsuperscript{CS117}. The aerial parts are smoked to decrease nausea and vomiting induced by anticancer drugs\textsuperscript{CS061}. Hot water extract of the aerial parts is taken orally by males as an aphrodisiac\textsuperscript{CS123}. The dried aerial parts are smoked by women to increase their amorous prowess\textsuperscript{CS181}. The fresh leaves are taken orally for hemorrhoids\textsuperscript{CS108}. Hot water extract of the dried leaf and seed is taken orally for stomach troubles and indigestion\textsuperscript{CS217}. Fresh leaf juice is administered intraural to treat earache\textsuperscript{CS143}. The fruit is used externally for skin diseases\textsuperscript{CS227}. The unripe fruit is taken orally to induce sleep\textsuperscript{CS181}.

Iran. Fluid extract of the dried flowering top or the dried fruit is taken orally for abdominal pain associated with indigestion, for pain associated with cancer, for rheumatoid arthritis, for gastric cramps or neuralgia, for coughing, and as a hypnotic. Fluid extract of the dried fruit is taken orally for whooping cough, as a hypnotic, and a tranquilizer\textsuperscript{CS234}. The dried seed is taken orally as a diuretic. An infusion is taken orally as an analgesic in rheumatism or rheumatoid arthritis, a sedative, a diaphoretic, and for hysterical conditions, gout, epilepsy, and cholera. The seed oil is administered per rectum to reduce cramps associated with lead poisoning associated with constipation and vomiting. To reduce breast engorgement or reduce milk secretion, the seed oil is applied topically. In some cases, it would completely stop milk secretion. One to 2 g of seed oil is taken orally several times a day for urinary incontinency\textsuperscript{CS234}.

Jamaica. Hot water extract of the flower, leaf, and twig is taken orally as an antispasmodic and anodyne\textsuperscript{CS238}. To eliminate cough, bronchitis, and other respiratory ailments, a half tablespoonful of powdered dried leaves is mixed with an equal amount of honey and taken orally three times daily\textsuperscript{CS193}. Seed oil is used externally for burns. The oil is extracted by roasting the seeds\textsuperscript{CS213}. Seeds are taken orally for diabetes, hysteria, and sleeplessness\textsuperscript{CS117}. The aerial parts are smoked to decrease nausea and vomiting induced by anticancer drugs\textsuperscript{CS061}. Hot water extract of the aerial parts is taken orally by males as an aphrodisiac\textsuperscript{CS123}. The dried aerial parts are smoked by women to increase their amorous prowess\textsuperscript{CS181}. The fresh leaves are taken orally for hemorrhoids\textsuperscript{CS108}. Hot water extract of the dried leaf and seed is taken orally for stomach troubles and indigestion\textsuperscript{CS217}. Fresh leaf juice is administered intraural to treat earache\textsuperscript{CS143}. The fruit is used externally for skin diseases\textsuperscript{CS227}. The unripe fruit is taken orally to induce sleep\textsuperscript{CS181}.

Mexico. The aerial parts are smoked as a hallucinogen\textsuperscript{CS117}.

Morocco. The aerial parts are taken orally as a narcotic\textsuperscript{CS111}.

Nepal. Decoction of the leaf is taken orally by adults as an anthelmintic\textsuperscript{CS090}. The powdered leaf is mixed with cattle feed as a treatment for diarrhea\textsuperscript{CS105}. For headache, the dried leaves are ground with Datura stramonium leaves and Picrorhiza schrophulariflora stem and water then applied externally\textsuperscript{CS221}. The leaf juice is used externally as an antiseptic, as a hemostat on cuts and wounds, and to treat swelling of sprained joints\textsuperscript{CS110}. The seeds are crushed, mixed with curd, and taken orally for dysentery\textsuperscript{CS090}. Decoction of the seed is taken orally as an anthelmintic\textsuperscript{CS104}. To aid in parturition, 2 teaspoonfuls of powdered seeds
are made into a paste with sesame oil (Sesamum indicum L.) and applied intra-vaginally during labor⁹⁹⁹.

**Pakistan.** Hot water extract of the entire plant is taken orally as a parturifacient⁹⁹⁸. Infusion of the leaf is taken orally for general weakness⁹⁹⁹.

**Saudi Arabia.** The aerial parts, mixed with honey, sugar, and nutmeg, are taken orally as a psychotropic⁹⁹⁸.

**Senegal.** The seed is taken orally as an emmenagogue⁹⁹⁹.

**South Africa.** Hot water extract of the entire plant is taken orally for asthma⁹⁹⁷. Hot water extracts of the root and seed are taken orally to induce abortion, labor, and menstruation⁹⁹⁸, ⁹⁹⁹.

**United States.** Fluid extract of the inflorescence is taken orally as a narcotic, antispasmodic, analgesic, and aphrodisiac⁹⁹⁹. Hot water extract of the flowering top is taken orally as a potent antispasmodic, anodyne, and narcotic. One teaspoon of plant material is steeped in 2 cups of boiling water, and 1 tablespoonful is taken two to four times a day⁹⁹⁹. The dried aerial parts are smoked by both sexes as an aphrodisiac⁹⁹⁹.

**Vietnam.** The seeds are taken orally as an emmenagogue⁹⁹⁹.

**West Indies.** Hot water extract of the entire plant is taken orally as an antispasmodic⁹⁹⁹.

**Yugoslavia.** Hot water extract of the seed is taken orally for diabetes⁹⁹⁹.

**Zimbabwe.** Hot water extract of the aerial parts is taken orally as a treatment for malaria⁹⁹⁹.

### CHEMICAL CONSTITUENTS

*(ppm unless otherwise indicated)*

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration</th>
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<tbody>
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<td>Acetaldehyde</td>
<td>Pl⁹⁹⁷</td>
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<tr>
<td>Acetone</td>
<td>Pl⁹⁹⁷</td>
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<tr>
<td>Actinidiolide, dihydro</td>
<td>EO⁹⁹⁶, Pl⁹⁹⁷</td>
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<tr>
<td>Alanine</td>
<td>Pl⁹⁹⁷</td>
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<tr>
<td>Aldotetronic acid, 2-C-methyl</td>
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<tr>
<td>Aldotetronolactone, 2-C-methyl</td>
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<tr>
<td>Anethole, cis</td>
<td>EO⁹⁹⁶, Pl⁹⁹⁷</td>
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<tr>
<td>Anethole, trans</td>
<td>EO⁹⁹⁶, Pl⁹⁹⁷</td>
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<tr>
<td>Apigenin glycoside</td>
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<td>Apigenin-7-O-para-coumaroyl-glucoside</td>
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<td>Behenic acid</td>
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<td>Benzaldehyde, para-ethyl</td>
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<td>Lf Smoke 3.3 µg/100 Cig⁹⁹⁸</td>
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<td>Lf Smoke 4.2 µg/100 Cig⁹⁹⁸</td>
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<td>Lf 5⁹⁹⁷, Aer⁹⁹⁷</td>
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<td>Bornesitol, D, (+)</td>
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<td>Butylamine, N</td>
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<td>Butylamine, sec</td>
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Butyraldehyde, iso: PlCS172
Cadaverine: PlCS172
Cadinene, Δ: PlCS172, EOCS156
Cadinene, γ: PlCS172, EOCS156
Calamenene: PlCS172, LfEOCS062
Campest-4-en-3-one: PlCS172
Campest-5-en-3-β-ol-7-one: PlCS172
Campestanol: SdCS076
Camphene hydrate: EOCS156, PlCS172
Camphene: Inflorescence EOCS156, LfEOCS062, ResinCS069
Camphor: LfEOCS062, PlCS172
Canabispiran: LfCS091
Cannabamine B: LfCS070
Cannabamine C: LfCS070
Cannabamine D: LfCS070
Cannabamine: LfCS070
Cannabicyclol: AerCS064, LfCS057, FlCS074, ResinCS043
Cannabinol methyl ether: ResinCS018
Cannabinol, Δ-6(A)-10(A)-tetrahydro, 10-oxo: ResinCS139, PlCS172
Cannabinol, Δ-6(A)-10(A)-tetrahydro, 8-9-dihydroxy (DL): AerCS158
Cannabinol, Δ-6(A)-10(A)-tetrahydro, 9-10-dihydroxy (DL): AerCS158
Cannabinol, Δ-6(A)-10(A)-tetrahydro, 9-hydroxy-10-ethoxy: AerCS118
Cannabinol, Δ-6(A)-10(A)-tetrahydro, cis: PlCS172
Cannabinol, Δ-8-tetrahydro, trans (−): AerCS064
Cannabinol, Δ-8-tetrahydro, trans: PlCS172
Cannabinol, Δ-8-tetrahydro: PlCS038, ResinCS035, ResinCS145, InflorescenceCS18
Cannabinol, Δ-9-tetrahydro, 6(A)-7-10(A)-trihydroxy: PlCS172
Cannabinol, Δ-9-tetrahydro, cis: LfCS114, Lf/FlCS074
Cannabinol, Δ-9-tetrahydro, methyl ether: ResinCS137
Cannabinol, Δ-9-tetrahydro, propyl: ResinCS137
Cannabinol, Δ-9-tetrahydro, trans (−): PlCS172
Cannabinol, Δ-9-tetrahydro, trans: PlCS172, ResinCS172
Cannabinol, Δ-9-tetrahydroxylic acid: ResinCS019
Cannabinol, hexahydro: AerCS064
Cannabinol, propyl: ResinCS137
Cannabinol, Δ-9-tetrahydroxylic acid: ResinCS019
Cannabinol, hexahydro: AerCS064
Cannabinol, propyl: ResinCS137
Cannabidiol, tetrahydro, iso: Resin$^{CS137}$
Cannabidiol, tetrahydro: Pl$^{CS131}$
Cannabinol: Resin$^{CS009}$, Sd 8$^{CS148}$, Fr 0.1275$^{CS089}$, Pl$^{CS038}$
Cannabinol-C-4, Δ9-tetrahydro, trans: Pl$^{CS172}$
Cannabinol-C-4: Pl$^{CS172}$
Cannabinolic acid A, Δ9-tetrahydro, trans (–): Aer$^{CS064}$
Cannabinolic acid A, Δ9-tetrahydro, trans: Pl$^{CS172}$
Cannabinolic acid A, Δ9-tetrahydro: Lf$^{CS004}$
Cannabinolic acid, Δ9-tetrahydro: Fl/Lf$^{CS074}$
Cannabinolic acid-C-4, Δ9-tetrahydro, trans: Pl$^{CS172}$
Cannabidiol, Δ6(A)-10(A)-tetrahydro, 9,10-dihydroxy (DL): Pl$^{CS172}$
Cannabiorcol, Δ9-tetrahydro, trans: Pl$^{CS172}$
Cannabiorcol: Pl$^{CS172}$
Cannabiorcolic acid, Δ9-tetrahydro, trans: Pl$^{CS172}$
Cannabipinol: Pl$^{CS172}$
Cannabiprene: Lf 26.8$^{CS091}$
Cannabiripsol: Pl$^{CS172}$, Aer$^{CS165}$
Cannabiserinone, anhydro: Pl$^{CS172}$
Cannabisin A: Fr 74$^{CS029}$
Cannabisin B: Fr 812$^{CS030}$
Cannabisin C: Fr 0.267$^{CS030}$
Cannabisin D: Fr 59.8$^{CS030}$
Cannabisin E: Fr 120$^{CS031}$
Cannabisin F: Fr 45$^{CS031}$
Cannabisin G: Fr 20$^{CS031}$
Cannabisiradienone: Pl$^{CS172}$
Cannabisperone, iso: Pl$^{CS172}$
Cannabispiradienon: Lf 5–6$^{CS185}$, CS001
Cannabispiran, dehydro: Lf 2.3$^{CS091}$, CS029
Cannabispiran, iso: Lf$^{CS180}$
Cannabispiran: Lf 20–24.5$^{CS080}$, CS029
Cannabispiranol, α: Lf 0.3$^{CS185}$
Cannabispiranol, β: Lf 8–80$^{CS209}$, CS091
Cannabispiran: Lf 18$^{CS157}$
Cannabispirenone A, (–): Lf 30$^{CS185}$
Cannabispirenone A, (DL): Lf 30$^{CS185}$
Cannabispirenone B: Lf$^{CS185}$
Cannabispirenone: Lf 210$^{CS185}$
Cannabispirenone: Lf 61$^{CS157}$, Aer 10$^{CS124}$
Cannabioptol, acetyl: Pl$^{CS172}$
Cannabiospernone: Aer 30$^{CS124}$, Pl$^{CS172}$, Lf 40$^{CS157}$
Cannabistilbene II: Lf 0.4$^{CS204}$
Cannabistilbene II: Lf$^{CS204}$
Cannabitetrol: Pl$^{CS205}$
Cannabithrene I: Lf 4$^{CS185}$
Cannabithrene II: Lf 8$^{CS185}$
Cannabitirol, (+): Aer$^{CS118}$, Pl$^{CS172}$
Cannabitirol, (+): Pl$^{CS172}$
Cannabitirol, (DL): Lf 2.7$^{CS203}$
Cannabitirol, trans (DL): Lf$^{CS194}$
Cannabitirol: Aer 250$^{CS079}$
Cannabivarichromene: Resin$^{CS017}$
Cannabivarin, Δ9-tetrahydro, trans (–): Pl$^{CS172}$, Aer$^{CS064}$
Cannabivarin, Δ9-tetrahydro, trans: Pl$^{CS172}$
Cannabivarin, tetrahydro: Fl/Lf$^{CS074}$
Cannabivarin: Pl$^{CS172}$
Cannabivarinic acid, Δ9-tetrahydro, trans (–): Aer$^{CS064}$
Cannabivarinic acid, Δ9-tetrahydro, trans: Pl$^{CS172}$
Cannabivarol, Δ9-tetrahydro: Pl$^{CS146}$
Cannabivarol, tetrahydro: Pl$^{CS041}$
Cannabivarol: Fl/tops$^{CS211}$
Cannabivarolic acid, tetrahydro: Pl$^{CS041}$
Cannflavin A: Aer 190$^{CS028}$
Cannflavin B: Aer 30$^{CS028}$
Cannflavin: Lf 138.5$^{CS027}$
Cannflavone 2: Aer$^{CS226}$
Cannflavone 1: Lf 0.8$^{CS185}$
Cannflavone 2: 6$^{CS185}$
Canniflavone: Lf 0.8$^{CS185}$
Car-3-ene: Inflorescence$^{CS156}$, EO$^{CS156}$, Pl$^{CS172}$
Car-4-ene: Pl$^{CS172}$, CS068
Carbazole: Lf (smoke)$^{CS054}$
Carvacrol: Lf EO$^{CS062}$, Pl$^{CS172}$
Carveol acetate, dihydro: Pl$^{CS172}$, EO$^{CS156}$
Carvone, dihydro: RtCS122, EOCS156, PI CS172
Carvone: RtCS122, EOCS156, PI CS172
Caryophyllene alcohol, α: EOCS156, PI CS068
Caryophyllene epoxide, β: Lf EO, Fl EOCS196
Caryophyllene epoxide: Lf EOCS062
Caryophyllene oxide: Fl tops CS111, Lf EOCS053, PI CS172
Caryophyllene, α: PI CS172, CS068
Caryophyllene, β: PI CS172, Resin CS069, Fl EOCS196, Inflorescence CS036
Caryophyllene, iso: PI CS172, Inflorescence EOCS036
Caryophyllene: Lf EOCS062
Castasterone: Sd CS071
Cedrene, α: Pl CS172, EOCS156
Cellulose, hemi: Pl CS172
Cholest-4-en-3-one, 24-methyl: Sd CS077
Cholest-5-en-3-one, 5-α, 24-methyl: Sd CS077
Cholesterol: Sd CS076
Choline: Pl CS172
Chrysene: Lf (smoke) 0.3 µg/100 Cig CS088
Cineol, 1-4: Pl CS172, Lf EOCS062
Cineol, 1-8: Lf EO CS062, PI CS172
Cinnamic acid, trans: Lf CS006, Pl CS172
Cinnamide, N-(para-hydroxy-β-phenylethyl)-para-hydroxy-(trans): PI CS172
Citric acid, iso: PI CS172
Citric acid: PI CS172
Citronelol: EOCS156, PI CS172
Copaeene, α: Lf EOCS062, PI CS172
Cosmosidoside: PI CS172
Coumaric acid, para: PI CS172
Cubebene, α: PI CS172, EOCS156
Curcumene, α: PI CS172, Lf EOCS062
Curcumene, β: PI CS172, CS068
Curcumene: EOCS156
Cyclocitral, β: PI CS172, EOCS156
Cyclohex-5-enone, 2-2-6-trimethyl: PI CS172, EOCS156
Cyclohexanone, 2-2-6-trimethyl: EOCS156, PI CS172
Cyclopentanost-24-methylene-3-β-acetate: PS033
Cymen-8-ol, para: EOCS156, PI CS172
Cymene, para: PI CS172, CS068, EOCS156, Inflorescence CS036
Cystine: PI CS172
Dec-3-en-5-one: EOCS156, PI CS172
Decan-1-ol: PI CS172, EOCS156
Decan-2-one: EOCS156, PI CS172
Decane, N: PI CS172
Dibenzo-(A-1)-anthracene: Lf (smoke) 0.3 µg/100 Cig CS088
Docosane, N: PI CS172
Dodecan-1-al: EOCS156, PI CS172
Dodecan-2-one: PI CS172, EOCS156
Dodecane, N: PI CS172
Dorotianone, 2-methyl: PI CS172
Dorotianone, N: PI CS172
Edestin: PI CS172
Edestinase: PI CS172
Eicosadienoic acid: PI CS172
Eicosane, N: PI CS172
Eicosenoic acid: PI CS172
Elemene, γ: EOCS156, Fl EO, Lf EOCS196, PI CS172
Ereptase (peptidase): PI CS172
Ergostan-3-one, 5-α: Call Tiss CS083
Ergosterol: PI CS172
Erythritol: PI CS172
Essential oil: Aer 0.09–0.11% CS156, Lf 0.15% CS062, Inflorescence CS036
Ethanol: PI CS172
Ethanolamine: PI CS172
Ethylamine, (DL): PI CS172
Ethylamine: PI CS172
Eudesmol, γ: EOCS156, PI CS172
Eugenol methyl ether: EOCS156, PI CS172
Eugenol, iso: EOCS156, PI CS172
Eugenol: EOCS156, PI CS172
Farnesene, α trans: trans: EOCS156, PI CS172
Farnesene, α: Fl EO, Lf EOCS196
Farnesene, β, cis: PI CS172
Farnesene, β: Fl EOCS196, Lf EOCS062, CS196
Farnesene, β: Resin CS069, Inflorescence EOCS036, EOCS156, PI CS172
Farnesene: PI CS172
Farnesol: PI CS172, EOCS156
Farnesene, α: PI CS172, EOCS156
Farnesene, α: Fl EO, Lf EOCS196
Farnesene, β: PI CS172
Farnesene, β, trans: Fl EOCS196, Lf EOCS062, CS196
Farnesene, β: Resin CS069, Inflorescence EOCS062, PI CS172
Farnesene: PI CS172
Fatty acids: Sd CS059
Fenchol: Lf EOCS062, PI CS068
Fenchone: EOCS156, PI CS172
Fenchyl alcohol: Resin CS069, EOCS156, PI CS172
Furfural, 5-methyl: EOCS156
Furan-2(5H)-one: Fl 0.6 µg/100 Cig CS182
Furo-(1,2-A)-4-N-penty1-7-7-10-trimethyl-dibenzopyran, 2-methyl: Lf (smoke) CS195
Furo-(1,2,A)-4-N-penty1-7-7-10-trimethyl-dibenzopyran-2-methyl: Lf (smoke) CS195
Furfural, 5-methyl: EOCS156
Furo-(1,2,A)-4-N-penty1-7-7-10-trimethyl-dibenzopyran-2-methyl: Lf (smoke) CS195
Furo-(1,2,A)-4-N-penty1-7-7-10-trimethyl-dibenzopyran: Lf (smoke) CS195
Furo-(1,2-A)-4-N-pentyl-7-7-10-trimethyl-dibenzopyran, 2-3-dimethyl: 
Lf (smoke) CS195
Galactitol: Pl CS172
Galactosamine: Pl CS172, Lf/St 1.9% CS081
Galactose: Pl CS172
Galacturonic acid: Pl CS172
Geraniol: Lf EO CS062, Pl CS172
Geranyl acetone: Pl CS172, EOC156
Glucaric acid: Pl CS172
Glucic acid: Pl CS172
Glucosamine: Pl CS172
Glucose, α (D): Pl CS172
Glucose, β (D): Pl CS172
Glutamic acid: Pl CS172
Glyceric acid: Pl CS172
Glycerol, (D), D-manno-octulose: Pl CS172
Glycerol: Pl CS172
Glycine: Pl CS172
Glycoprotein (Cannabis sativa): Lf CS119
Grossamide: Fr CS029
Gurjene, α: Fl EO CS196, Resin CS069, Pl CS172
Heneicosane, 3-methyl: Pl CS172
Heneicosane, N: Pl CS172
Hentriacontane, 2-methyl: Pl CS172
Hentriacontane, 3-methyl: Pl CS172
Hentriacontane, N: Pl CS172
Hept-2-3n-6-one, 2-methyl: Pl CS172
Hept-5-en-2-one, 6-methyl: EO CS156
Heptacosane, 3-methyl: Pl CS172
Heptacosane, N: Aer CS063, Pl CS172
Heptadecane, 3-6-dimethyl: Pl CS172
Heptadecane, 3-7-dimethyl: Pl CS172
Heptadecane, N: Pl CS172
Heptan-1-al: Pl CS172, EOC156
Heptan-2-one: EO CS156, Pl CS172
Hexacosane, 2-methyl: Pl CS172
Hexacosane, N: Pl CS172
Hexadecanamide: Resin CS116
Hexadecane, N: Pl CS172
Hexadecane-1-ol: Pl CS172, EOC156
Hexan-1-al: EOC156, Pl CS172
Hexan-1-ol acetate: Pl CS172
Hexan-1-ol butyrate: Pl CS172
Hexan-1-ol caproate: Pl CS172
Hexan-1-ol iso-butyrate: Pl CS172
Hexatriacontane, N: Pl CS172
Hex-cis-3-en-1-ol caproate: EOC156
Hex-cis-3-enol caproate: Pl CS172
Hexyl acetate: EO CS156
Hexyl iso-butyrate: EO CS156
Histamine: Pl CS172
Histidine: Pl CS172
Hordenine: Lf CS051, Pl CS172
Humulene oxide I: Pl CS172
Humulene oxide II: Pl CS172
Humulene oxide: EO CS156
Humulene, α: Lf EO, Fl EOC196
Humulene, β: Pl CS172, Inflorescence EOC156
Humulene, β: Pl CS172, Inflorescence EOC156
Indan-1-spiro-cyclohexane, 5-7-dihydroxy: 
Resin CS026
Indan-1-spiro-cyclohexane, 5-hydroxy-7-methoxy: Resin CS026
Indan-1-spiro-cyclohexane, 7-hydroxy-5-methoxy: Resin CS026
Indole: Lf (smoke) CS054
Inositol, (+): Pl CS172
Inositol, myo: Pl CS172, Fl/Lf CS082
Ionone, β: EOC156, Pl CS172
Kaempferol: Aer CS241
Ledol: Pl CS172, EOC156
Leucine, iso: Pl CS172
Leucine: Pl CS172
Lignanamide I: Fr CS093
Limonene: Pl CS172, Fl EOC196, Resin CS069, Pl CS172
Linoleic acid methyl ester: Pl CS172, Sd CS134
Linolenic acid methyl ester: EOC156
Linolenic acid: Pl CS172, Sd CS134
Longifolene, (+): Pl CS068
Longifolene: Pl CS172, EOC156, Inflorescence EOC156
Lysine: Pl CS172
Methanol: Pl CS172
Methionine: Pl CS172
Methyl acetate: Pl CS172
Methylamine, di: Pl CS172
Muscarine: Pl CS172
Myrcene: Fl EO CS156, Resin CS069, Inflorescence EO CS156, Pl CS069
Myristic acid: Pl CS172, EO CS156
Nerol: EO CS062, Pl CS172
Nerolidol: Lf EO CS062, Pl CS172
Neurine: Pl CS172, Rt CS070
Neurine: Pl CS172, Rt CS070
Nerolidol: Lf EO CS062, Pl CS172
Nonacosane: Aer CS063, Pl CS172
Nonadecane: Pl CS172
Nonan-1-al: Pl CS172, EO CS156
Nonan-1-ol: Pl CS172, EO CS156
Nonane: Pl CS172
Nonatriacontane: Pl CS172
Ocimene, β, cis: Pl CS172, EO CS156
Ocimene, β, trans: Lf EO CS062, Pl CS172, CS068
Oxidase, polyphenol: Pl CS172
Palmitic acid methyl ester: Call Tiss CS083, EO CS156, Pl CS172
Palmitic acid: Sd CS134, Pl CS172
Palmitoleic acid: Pl CS172
Pectin: Pl CS172
Pentacosane, 3-methyl: Pl CS172
Pentacosane, N: Pl CS172
Pentadecan-2-one, 6-10-14-trimethyl: Pl CS172, EO CS156
Pentadecane: Pl CS172
Pentan-1-ol: EO CS156, Pl CS172
Pentatriacontane, N: Pl CS172
Phellandrene, α: Inflorescence EO CS156, Pl CS172
Phellandrene, β: Lf EO CS062, Pl CS172
Piperidine: Fl top, Lf CS070, Pl CS172
Piperitenone oxide: EO CS156, Pl CS172
Piperitenone: Resin CS069, EO CS156, Pl CS172
Piperitone oxide: EO CS156, Pl CS172
Pinene, α: Inflorescence EO CS156, Lf EO CS062, Pl CS172
Pinene, β: Lf EO CS062, Resin CS069, Inflorescence EO CS156, Pl CS172
Pisatin: Pl CS172
Pyrano-(3-4-B)-benzofuran, 1-4 5-hydroxy-7-pentyl-1-(A)-α-3-3-trimethyl-ethano-1-(H): Aer CS115
Pyrene: Lf (smoke) 6.6 µg/Cig CS088
Quebrachitol, (+): Pl CS172
Quercetin: Aer CS241, Pl CS172
Raffinose: Pl CS172
Rhamnose: Pl CS172
Ribitol: Pl CS172
Ribose: Pl CS172
Sabine, trans: Pl CS172, EO CS156
Sabine, EO: CS156, Pl CS172
Safranal: EO CS156, Pl CS172
Sabinene, trans: Pl CS172, EO CS156
Sabinene: EO CS156, Pl CS172
Salicylic acid methyl ester: EO CS156, Pl CS172
Santalene, β, epi: Pl CS172, EO CS156
Sativic acid: Pl CS172
Scyllitol: Fl/Lf CS082
Selina-3-7(11)-diene: Pl CS172, Inflorescence EO CS036
Selina-4(14)-7(11)-diene: Inflorescence EO CS036, Pl CS172
Selina-4(11)-7(11)-diene: Inflorescence EO CS036, Pl CS172
Selinene, α: Pl CS172, Inflorescence EO CS036, EO CS156
Selinene, β: Inflorescence EO CS036, Pl CS172, EO CS156
Serine: Pl CS172
Sitostanol: Sd CS076
Sitosterol, β: Rt CS122, Sd CS076, Call Tiss CS083, Pl CS172
Skatole: Lf (smoke) CS054
Sorbitol: Pl CS172
Spiro-(cyclohexane-1-3-(4-6-dihydroxy-indan): Fl top CS135
Spiro-(cyclohexane-1-3-(4-hydroxy-6-methoxy-indan): Fl top CS135
Spiro-(cyclohexane-1-3-(6-hydroxy-4-methoxy-indan): Fl top CS135
Stearic acid methyl ester: Call Tiss CS083
Stearic acid: Pl CS172, Sd CS134
Stigmaster-22-en-3-one, 5-α: Call Tiss CS083
Stigmaster-4-en, 3-one: Pl CS172, Rt CS050
Stigmaster-5-en-3-β-ol-7-one: Rt CS050, Pl CS172
Stigmast-4-22-diene-3-one: Rt CS050, Pl CS172
Stigmast-5-22-dien-3-β-ol-7-one: Rt CS050
Stigmasta-7-24(28)-dien-3-β-ol, 5-α: Pl CS172
Stigmastan-3-one, 5-α: Call Tiss CS083
Stigmasterol: Sd CS076 Pl CS172
Stillbene, dihydro 3'-5-dihydroxy-3,4-dimethoxy: Lf CS185
Stillbene, dihydro 4'-5-dihydroxy-3,4-dimethoxy: Lf CS185
Sucinic acid: Pl CS172
Sucrose: Pl CS172
Terpinen-4-ol, α: Pl CS172
Terpinen-4-ol: Lf EO CS062, Pl CS172
Terpinene, α: Lf EO CS062, Pl CS172, Inflorescence EO CS036
Terpinene, γ: Pl CS172, Resin CS069, EO CS156, Inflorescence EO CS036
Terpineol, α: Pl CS172, Resin CS069, Lf EO CS062, EO CS156
Terpineol, β: EO CS156, Pl CS172
Terpinolene: Fl EO CS062, Lf EO CS062, Inflorescence EO CS036, Pl CS172
Tetracosane, 2-methyl: Pl CS172
Tetracosane, N: Pl CS172
Tetradecane, 2,6-dimethyl: Pl CS172
Tetradecane, N: Pl CS172
Tetratriacontane, N: Pl CS172
Threonic acid: Pl CS172
Threonine: Pl CS172
Thujene, α: Pl CS172, CS068, EO CS156
Thujol alcohol: Pl CS172, EO CS156
Triacanone, 3-methyl: Pl CS172
Triacanone, N: Pl CS172
Tricosane, 3-methyl: Pl CS172
Tricosane, N: Pl CS172
Tridecan-1-al: EO CS156, Pl CS172
Tridecane, 3-6-dimethyl: Pl CS172
Tridecane, N: Pl CS172
Trigonelline: Pl CS172, Fl top CS070
Tritriacontane, N: Pl CS172
Tryptophan: Pl CS172
Tyramine, feruloyl: Sd 2.5, Rt, Resin, Lf CS149, CS230
Tyramine, N-(para-coumaroyl): Fr 111 CS029, Sd 111 CS092
Tyramine, N-trans-caffeoyl: Fr 47.1 CS029
Tyramine, N-trans-feruloyl: Fr 78.5 CS029
Tyramine, para-coumaroyl: Sd 0.5 CS230, Rt, Lf, Resin CS149, CS230
Tyramine, N: Pl CS172
Tyrosine: Pl CS172
Undecan-1-al: EO CS156, Pl CS172
Undecan-2-one, 6-10-dimethyl: EO CS156, Pl CS172
Undecan-2-one: EO CS156, Pl CS172
Undecane, N: Pl CS172
Valine: Pl CS172
Vanillic acid: Pl CS172
Vitamin K: Pl CS172
Vitexin, iso, 7-O-α-L-rhamnosyl-glucoside: Pl CS172
Vitexin, iso, 7-O-β-D-glucosyl-arabinoside: Pl CS172
Vitexin, iso, 7-O-β-D-glucosyl-arabinoside: Pl CS172
Xylose: Pl
Zeatin nucleoside: Pl
Zeatin: Pl

PHARMACOLOGICAL ACTIVITIES AND CLINICAL TRIALS

Abortifacient activity. Alcohol extract of the dried leaf, administered intragastrically to pregnant rats at a dose of 125 mg/kg, produced teratogenic effects. Water extract of the dried leaf, administered intragastrically to pregnant rats at variable dosage levels on days 6–15 of pregnancy was active.

Acute cardiovascular fatalities. Six cases of possible acute cardiovascular death in young adults were reported where very recent cannabis ingestion was documented by the presence of Δ-9-tetrahydrocannabinol (Δ-9-THC) in postmortem blood samples. A broad toxicological blood analysis could not reveal other drugs.

Acute panic reaction (Koro). Koro, an acute panic reaction related to the perception of penile retraction, was once considered limited to specific cultures. Over 70 American men responded by telephone to report negative reactions to cannabis. Three of them (Caucasians aged 22–26 years with considerable experience with cannabis) spontaneously mentioned experiencing symptoms of Koro after smoking cannabis. All three cases occurred after the participants had heard about cannabis-induced Koro and used the drug in a novel setting or atypical way. Two of the men had body dysmorphia, which may have contributed to symptoms. All three decreased their cannabis consumption after the Koro experience. Several factors may have interacted to create the symptoms. These include previous knowledge of cannabis-induced Koro, the use of cannabis in a way that might heighten a panic reaction, and poor body image.

Adverse effects. A causal role of acute cannabis intoxication in motor vehicle and other accidents has been shown by the presence of measurable levels of Δ-9-THC in the blood of drivers in the absence of alcohol or other drugs, by surveys of driving under the influence of cannabis, and by significantly higher accident culpability risk of drivers using cannabis. Evidence demonstrated that cannabis dependence, both behavioral and physical, occurred in about 7–10% of regular users, and that early onset of use—especially of weekly or daily use—is a strong predictor of future dependence. Cognitive impairments of various types are readily demonstrable during acute cannabis intoxication, but there is no suitable evidence yet available to permit a decision as to whether long-lasting or permanent functional losses can result from chronic heavy use in adults. The gender effects on progression to treatment entry and on the frequency, severity, and related complications of the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised drug and alcohol dependence among 271 substance-dependent patients (mean age: 32.6 years; 156 women) was studied. There was no gender difference among patients in the age at onset of regular use of any substance. Women experienced fewer years of regular use of opioids and cannabis and fewer years of regular alcohol drinking before entering treatment. Although the severity of drug and alcohol dependence did not differ by gender, women reported more severe psychiatric, medical, and employment complications. In a 3-day, double-blind, randomized, counterbalanced study, the behavioral, cognitive, and endocrine effects of 2.5 and 5 mg intravenous Δ-9-THC were characterized in 22 healthy individuals, who had been exposed to cannabis but had never been diagnosed with a cannabis abuse disorder. Prospective safety data at 1, 3, and 6 months post-study was also analyzed. Δ-9-THC produced schizophrenia-like positive and negative symptoms, altered perception, increased anxiety and plasma cortisol,
euphoria, disrupted immediate and delayed word recall, sparing recognition recall, impaired performance on tests of distractibility, verbal fluency, and working memory, but did not impair orientation. This study examined the behavioral and neurochemical (cannabinoid CB1 receptor gene expression) changes induced by spontaneous cannabinoid withdrawal in mice. Cessation of CP-55,940 treatment in tolerant mice induced a spontaneous time-dependent behavioral withdrawal syndrome consisting of marked increases (140%) in motor activity, number of rearings (170%), decreases in grooming (57%), wet-dog shakes (73%), and rubbing behaviors (74%) on day 1, progressively reaching values similar to vehicle-treated mice on day 3. This spontaneous cannabinoid withdrawal resulted in CB1 gene expression up-regulation (20–30%) in caudate-putamen, ventromedial hypothalamic nucleus, central amygdaloid nucleus, and CA1, whereas in the CA3 field of hippocampus, a significant decrease (15–20%) was detected.

**Alcohol interaction.** The complementary DNA and genomic sequences encoding G protein-coupled cannabinoid receptors (CB1 and CB2) from several species were cloned. This has facilitated discoveries of endogenous ligands (endocannabinoids). Two fatty acid derivatives characterized to be arachidonylethanolamide and 2-arachidonylglycerol isolated from both nervous and peripheral tissues mimicked the pharmacological and behavioral effects of Δ-9-THC. The down-regulation of CB1 receptor function and its signal transduction by chronic alcohol was demonstrated. The observed down-regulation of CB1 receptor-binding and its signal transduction resulted from the persistent stimulation of receptors by the endogenous CB1 receptor agonists arachidonylethanolamide and 2-arachidonylglycerol, whose synthesis is increased by chronic alcohol treatment. The deletion of CB1 receptor has been shown to block voluntary alcohol intake in mice.

**Allergenic effect.** An “All India Coordinated Project on Aeroallergens and Human Health” was undertaken to discover the quantitative and qualitative prevalence of aerosols at 18 different centers in the country. Predominant airborne pollens were Holoptelea, Poaceae, Asteraceae, Eucalyptus, Casuarina, Putanjiva, Cassia, Quercus, Cocos, Pinus, Cedrus, Ailanthus, Chenoi/Amaranth, Cyperus, Argemone, Xanthium, Parthenium, and others. Clinical and immunological evaluations revealed some allergenically important taxa. Allergenically important pollens were Prosopis juliflora, Ricinus communis, Morus, Mallotus, Ailanthus, Quercus, Cedrus, Argemone, Amaranthus, Chenopodium, Holoptelea, Brassica, Cocos, Cannabis, Parthenium, Cassia, and grasses. In the multitest routine skin-test battery, 78 of 127 patients tested (61%) were cannabis-test positive. Thirty of the 78 patients were randomly selected to determine if they had allergic rhinitis and/or asthma symptoms during the cannabis pollination period. By history, 22 (73%) claimed respiratory symptoms in July through September. All 22 of these subjects were also skin test-positive to weeds pollinating during the same period as cannabis (ragweed, pigweed, cocklebur, Russian thistle, marsh elder, or kochia).

**Alkaline phosphatase stimulation.** Ethanol (95%) extract of the dried resin, administered intraperitoneally to toads at a dose of 10 mg/day for 14 days, was active. The results were significant at $p < 0.01$ level.

**Aminopyrene-N-demethylase induction.** Ethanol (95%) extract of the dried aerial parts, administered intraperitoneally to rats at a dose of 2 mg/kg for 15 days, was active. A dose of 20 mg/kg for 7 days was also active.

**Amnesic syndrome.** A 26-year-old woman suffered disseminated intravascular coagulation (DIC) and a brief respiratory arrest fol-
lowing recreational use of 3,4-methylenedioxymethamphetamine (MDMA, or “ecstasy”) together with amyl nitrate, lysergic acid (LSD), cannabis, and alcohol. She was left with residual cognitive and physical deficits, particularly severe anterograde memory disorder, mental slowness, severe ataxia, and dysarthria. Follow-up investigations have shown that these have persisted, although there has been some improvement in verbal recognition memory and in social functioning. Magnetic resonance imaging and quantified positron emission tomography investigations revealed severe cerebellar atrophy and hypometabolism accounting for the ataxia and dysarthria; thalamic, retrosplenial, and left medial temporal hypometabolism to which the anterograde amnesia can be attributed. There was some degree of frontotemporal–parietal hypometabolism, possibly accounting for the cognitive slowness. The putative relationship of these abnormalities to the direct and indirect effects of MDMA toxicity, hypoxia, and ischemia was considered.

**Amyotrophic lateral sclerosis.** One hundred thirty-one respondents with amyotrophic lateral sclerosis—13 of whom reported using cannabis in the last 12 months—were examined. The results indicated that cannabis might be moderately effective at reducing symptoms of appetite loss, depression, pain, spasticity, and drooling. Cannabis was reported ineffective in reducing difficulties with speech and swallowing, and sexual dysfunction. The longest relief was reported for depression (approx 2–3 hours).

**Analgesic activity.** Ethanol (50%) extract of the entire plant, administered intraperitoneally to mice at a dose of 250 mg/kg, was active vs tail pressure method. Flavonoid fraction of the leaf, administered intraperitoneally to mice, was active vs phenylbenzoquinone-induced writhing, inhibitory concentration (IC)50 0.013 mg/kg and 0.045 mg/kg, respectively. Petroleum ether and ethanol (95%) extracts of the dried aerial parts, administered intragastrically to mice, was active vs phenylbenzoquinone-induced writhing, inhibitory concentration (IC)50 0.013 mg/kg and 0.045 mg/kg, respectively.

**Analgesic effect.** Ajulemic acid (AJA, CT-3, or IP-751), administered to healthy human adults and patients with chronic neuropathic pain, demonstrated a complete absence of psychotropic actions. It proved to be more effective than placebo in reducing this type of pain as measured by the visual analog scale. Signs of dependency were not observed after withdrawal at the end of the 1-week treatment period.

Forty women undergoing elective abdominal hysterectomy were investigated in a randomized, double-blind, placebo-controlled, single-dose trial. Randomization took place when postoperative patient-controlled analgesia was discontinued on the second postoperative day. When patients requested further analgesia, they received a single, identical capsule of either 5 mg of oral Δ9-THC (n = 20) or placebo (n = 20) in a double-blind fashion. The primary outcome measure was summed pain intensity difference (SPID) at 6 hours after administration of the study medication derived from visual analog pain scores on movement and at rest. Secondary outcome measures were time-to-rescue medication and adverse effects of study medication. Mean (standard deviation [SD]) visual analog scale pain scores before medication in the placebo and Δ9-THC groups were 6.3(2.6) and 6.4(1.3) cm on movement, and 3.2(1.9) and 3.3(0.9) at rest, respectively. There were no significant differences in mean (95% confidence interval [CI] of the difference) SPID at 6 hours between the groups (placebo 7.9, Δ9-THC 4.3[−1.8 to 9] cm per hour on movement; placebo 8.8, Δ9-THC 4.9[−0.2 to 8.1] cm
per hour at rest) and time to rescue analgesia (placebo 217, Δ-9-THC 163[–22 to 130] minutes). Increased awareness of surroundings was reported more frequently in patients receiving Δ-9-THC (40 vs 5%, \( p = 0.04 \)). There were no other significant differences with respect to adverse events. THC, morphine, and a THC–morphine combination were administered to 12 healthy subjects using experimental pain models (heat, cold, pressure, and single and repeated transcutaneous electrical stimulation). THC (20 mg), morphine (30 mg), THC–morphine (20 mg THC + 30 mg morphine), or placebo were given orally as single dose. Reaction time, side effects (visual analog scales), and vital functions were monitored. For the pharmacokinetic profiling, blood samples were collected. THC did not significantly reduce pain. In the cold and heat tests, it even produced hyperalgesia, which was completely neutralized by THC–morphine. A slight additive analgesic effect was observed for THC–morphine in the electrical stimulation test. No analgesic effect resulted in the pressure and heat test, with neither THC nor THC–morphine. Psychotropic and somatic side effects (sleepiness, euphoria, anxiety, confusion, nausea, dizziness, etc.) were common, but usually mild. Three cannabis-based extracts Δ-9-THC, cannabidiol [CBD], and a 1:1 mixture of them both) were given over a 12-week period in a randomized, double-blind, placebo-controlled, crossover trial. Extracts, which contained THC, proved most effective in symptom control. Regimens for the use of the sublingual spray emerged and a wide range of dosing requirements was observed. Side effects were common, reflecting a learning curve for both patient and study team. These were generally acceptable and little different to those seen when other psychoactive agents are used for chronic pain. Over a 6-week period 209 chronic noncancer pain patients were studied. Seventy-two (35%) subjects reported ever having used cannabis. Thirty-two (15%) subjects reported having used cannabis for pain relief (pain users), and 20 (10%) subjects were currently using cannabis for pain relief. Thirty-eight subjects denied using cannabis for pain relief (recreational users). Compared with nonusers, pain users were significantly younger (\( p = 0.001 \)) and were more likely to be tobacco users (\( p = 0.0001 \)). The largest group of patients using cannabis had pain caused by trauma and/or surgery (51%), and the site of pain was predominantly neck/upper body and myofascial (68 and 65%, respectively). The median duration of pain was similar in both pain users and recreational users (8 vs 7 years; \( p = 0.7 \)). There was a wide range of amounts and frequency of cannabis use. Of the 32 subjects who used cannabis for pain, 17 (53%) used four puffs or less at each dosing interval, eight (25%) smoked a whole cannabis cigarette (joint), and four (12%) smoked more than one joint. Seven (22%) of these subjects used cannabis more than once daily, five (16%) used it daily, eight (25%) used it weekly, and nine (28%) used it rarely. Pain, sleep, and mood were most frequently reported as improving with cannabis use, and “high” and dry mouths were the most commonly reported side effects. Patients with chronic pain completed a questionnaire about the type of cannabis used, the mode of administration, the amount used and the frequency of use, and their perception of the effectiveness of cannabis on a set of pain-associated symptoms and side effects. Fifteen patients (10 males) were interviewed (median age, 49.5 years; range, 24–68 years). All patients smoked herbal cannabis for therapeutic reasons (median duration of use, 6 years; range, 2 weeks–37 years). Seven patients only smoked at night (median dose eight puffs, range two to eight puffs), and eight patients used cannabis mainly during the
day (median dose of three puffs; range, two to eight puffs); the median frequency of use was four times per day (range, 1 to 16 times/day). Twelve patients reported improvement in pain and mood, whereas 11 reported improvement in sleep. Eight patients reported a “high;” six denied a “high.” Tolerance to cannabis was not reported. THC was administered to six patients with chronic pain at doses 5–20 mg/day. A sufficient pain relief had been achieved in three patients. The other three suffered from intolerable side effects, such as nausea, dizziness, and sedation without a reduction of pain intensity. In these cases, the treatment was continued with other analgesics.

**Anaphrodisiac effect.** Tincture of the resin, administered intraperitoneally to male mice at a dose of 12.5 mg/kg, produced a significant reduction in mounts and attempted mounts. Other behavioral activities were unaffected.

**Angiotensin-converting enzyme inhibition.** Ethanol (100%) extract of the dried leaf at a concentration of 333.3 µg/mL produced weak activity, and the water extract was inactive.

**Ankylosing spondylitis.** Ankylosing spondylitis is a systemic disorder occurring in genetically predisposed individuals. The disease course appears to be characterized by bouts of partial remission and flares. There were 214 patients questioned (169 men, 45 women; average disease duration, 25 years; age of disease onset, 22 years). The main symptoms of flare were pain (all groups), immobility (90%), fatigue (80%), and emotional symptoms, such as depression, withdrawal, and anger, (75%). All of patients experienced between one and five localized flares per year. Fifty-five percent of the groups contained patients (n = 85) who experienced a generalized flare. The main perceived triggers of flare were stress (80%) and “overdoing it” (50%). Patients reported that a flare might last anywhere from a few days to a few weeks and relief from flare were by analgesic injections (including opiates), relaxation, sleep, and cannabis (three individuals). Three-quarters of the groups agreed that there was no long-term effect on the ankylosing spondylitis following a flare.

**Anti-anaphylactic activity.** Water extract of the dried fruit, at a concentration of 1 µg/mL, produced weak activity on the rat Leuk-RBL 2H3 vs biotinyl immunoglobulin E-avidin complex-induced degranulation of β-hexosaminidase.

**Anti-androgenic effect.** Ethanol (95%) extract of the aerial parts, administered intraperitoneally to castrated mice at a dose of 2 mg/animal, produced strong activity. The dried leaf, smoked by 13 male adults for 21 days, was inactive.

**Anti-arthritic effect.** Oral administration of AJA, a cannabinoid acid devoid of psychoactivity, reduced joint tissue damage in rats with adjuvant arthritis. Peripheral blood monocytes (PBM) and synovial fluid monocytes (SFM) were isolated from healthy subjects and patients with inflammatory arthritis, respectively, treated with AJA (0–30 mM) in vitro, and then stimulated with lipopolysaccharide. Cells were harvested for messenger RNA (mRNA), and supernatants were collected for cytokine assay. Addition of AJA to PBM and SFM in vitro reduced both steady-state levels of interleukin-1γ (IL-1γ) mRNA and secretion of IL-1γ in a concentration-dependent manner. Suppression was maximal (50.4%) at 10 mM AJA (p < 0.05 vs untreated controls, n = 7). AJA did not influence tumor necrosis factor-α (TNF-α) gene expression in or secretion from PBM.

**Antibacterial activity.** Essential oil, on agar plate, was active on *Staphylococcus aureus* and *Streptococcus faecalis*, minimum inhibitory concentration (MIC) 0.5 mg/mL.
and produced weak activity on *Pseudomonas fluorescens* and *Escherichia coli*, MIC 10 mg/mL and 5 mg/mL, respectively. Anticonvulsant activity. Ethanol (95%) extract of the entire plant, administered subcutaneously to male mice and rats at a dose of 2–4 mL/kg, was active vs metrazole and electroshock, respectively. A dose of 4 mL/kg was inactive vs strychnine convulsions in mice. The entire plant, smoked by 29 patients with epilepsy under the age of 30 years, was active. It must be noted that in some species, cannabinoids can precipitate epileptic seizures. Tincture of the resin, administered intraperitoneally to mice at a dose of 25 mg/kg, produced 80% protection vs pentylenetetrazole convulsions.

Antidiuretic activity. After ingesting the aerial parts, a 55-year-old man developed urinary retention that required catheterization for relief.

Anti-emetic activity. In a qualitative study of self-care in pregnancy, birth, and lactation within a nonrandom sample of 27 women in British Columbia, Canada, 20 women (74%) experienced pregnancy-induced nausea. Ten of these women used antiemetic herbal remedies, which included ginger, peppermint, and cannabis. Only ginger has been subjected to clinical trials among pregnant women, although the three herbs were clinically effective against nausea and vomiting in other contexts, such as chemotherapy-induced nausea and post-operative nausea. CBD, a major non-psychoactive cannabinoid administered by oral infusion to rats with nausea elicited by lithium chloride, and with conditioned nausea elicited by a flavor paired with lithium chloride, was active. Oral nabilone, oral dronabinol (THC), and intramuscular levonantradol were administered to 1366 patients. Cannabinoids were more effective antiemetics than prochlorperazine, metoclopramide, chlorpromazine, thienylperazine, haloperidol, domperidone, or alizapride. Relative risk was 1.38 (95% CI 1.18–1.62), number-needed-to-treat (NNT) was 6 for complete control of nausea; relative risk was 1.28 (CI 1.08–1.51), NNT 8 for complete control of vomiting. Cannabinoids were not more effective in patients receiving very low or very high emetogenic chemotherapy. In crossover trials, patients preferred cannabinoids for future chemotherapy cycles: relative risk 2.39 (2.05–2.78), NNT 3. Some potentially beneficial side effects occurred more often with cannabinoids: “high” 10.6 (6.86–16.5), NNT 3; sedation or drowsiness 1.66 (1.46–1.89), NNT 5; euphoria 12.5 (3–52.1), NNT 7. Harmful side effects also occurred more often with cannabinoids: dizziness 2.97 (2.31–3.83), NNT 3; dysphoria or depression 8.06 (3.38–19.2), NNT 8; hallucinations 6.10 (2.41–15.4), NNT 17; paranoia 8.58 (6.38–11.5), NNT 20; and arterial hypotension 2.23 (1.75–2.83), NNT 7. Patients given cannabinoids were more likely to withdraw because of side effects (relative risk 4.67 [3.07–7.09]; NNT 11).

Anti-estrogenic effect. Ethanol (95%) extract of the dried aerial parts, administered intragastric to rats at variable doses was inactive. Petroleum ether extract of the dried leaf, administered intraperitoneally to female rats at a dose equivalent to 10 mg/kg tetrahydrocannabinol (THC) on 11–21 days of age, was active. Resin, administered by gastric intubation to male mice at variable dosage levels, was inactive. Antifertility effect. Petroleum ether extract of the entire plant, administered by gastric intubation to female mice at doses of 75 mg/kg and 150 mg/kg, was active. A dose of 3 mg/kg, produced weak activity. Resin, administered by gastric intubation to male mice at variable dosage levels, was inactive. Antifungal activity. Ethanol (50%) extract of the dried leaf was active on *Rhizoctonia solani*, mycelial inhibition was 65.99%.
at a concentration of 1:1 was active on *Fusarium oxysporum*<sub>CS096</sub>. The water extract also produced strong activity on *Ustilago maydis* and *Ustilago nuda*<sub>CS112</sub>. Water extract of the fresh shoot on agar plate was inactive on *Helminthosporium turcicum*<sub>CS217</sub>.

**Antiglaucomic activity.** Water extract of the dried entire plant, administered intravenously to Rhesus monkeys and rabbits at a dose of 0.01 µg/animal, was active. The intraocular pressure rose for 24 hours postinjection, then fell for 3 days. A dose of 25 µg/animal, administered intravenously to rabbits, was also active. The effect was not influenced by atropine, scopolamine, methysergide, haloperidol, chlorpromazine, spironolactone, yohimbine or dexamethasone. Partial inhibition was seen when galactose, glucose or mannose were administered intravenously, concurrently<sup>CS212</sup>. Water extract of the dried leaf and stem, applied ophthalmically to rabbits was active<sup>CS072</sup>.

**Antigonadotropin effect.** Ethanol (80%) extract of the dried aerial parts, administered intragastrically to male langurs at a dose of 14 mg/kg daily for 90 days produced equivocal effect<sup>CS173</sup>.

**Anti-inflammatory activity.** Petroleum ether and ethanol (95%) extracts of the dried aerial parts, applied externally on mice at a dose of 100 µg/ear, was active vs tissue plasminogen activator-induced erythema of the ear<sup>CS140</sup>. CBD was administered orally to rats at doses of 5–40 mg/kg daily for 3 days after the onset of acute inflammation induced by intraplantar injection of 0.1 mL carrageenan (1% w/v in saline). CBD had a time- and dose-dependent antihyperalgesic effect after a single injection. Edema following carrageenan peaked at 3 hours and lasted 72 hours. A single dose of CBD reduced edema in a dose-dependent fashion and subsequent daily doses produced further time- and dose-related reductions. There were decreases in prostaglandin E2 (PGE2) plasma levels, tissue cyclo-oxygenase activity, production of oxygen-derived free radicals, and nitric oxide (NO), nitrite/nitrate content after three doses of CBD. The effect on NO seemed to depend on a lower expression of the endothelial isoform of NO synthase<sup>CS303</sup>.

**Antimalarial activity.** The dried leaf was inactive on *Plasmodium falciparum* D-6 and W-2, IC<sub>50</sub> greater than 1000 nmols<sup>CS095</sup>.

**Antimycobacterial activity.** Essential oil, on agar plate, was active on *Antimycobacterium smegmatis*, MIC 0.1 mg/mL<sup>CS132</sup>.

**Antinematodal activity.** Water extract of the dried leaf at variable concentrations produced strong activity on *Meloidogyne incognita*<sup>CS200</sup>.

**Antioxidant activity.** Methanol extract of the stem, at concentration 50 µL, produced strong activity<sup>CS101</sup>.

**Antispasmodic activity.** Ethanol (50%) extract of the entire plant was active on the guinea pig ileum vs acetylcholine and histamine-induced spasms<sup>CS007</sup>. The resin antagonized serotonin contractions of the rat intestine and non-pregnant uterus<sup>CS003</sup>.

**Antispermatogenic effect.** Sixteen healthy chronic marijuana smokers were associated with a decline in sperm concentration and total sperm count during the fifth and sixth weeks after 4 weeks of high-dose smoking (8–20 cigarettes/day)<sup>CS164</sup>. The dried aerial part, taken by inhalation daily, decreases the quantity as well as quality of spermatozoa<sup>CS181</sup>. Ethanol (80%) extract of the dried aerial parts, administered intraperitoneally to mice at a dose of 2 mg/animal daily for 45 days, produced a complete arrest of spermatogenesis. The effect was reversible<sup>CS244</sup>.

**Antistress activity.** The leaf smoke, in combination with hashish smoke, administered to rats housed in a wire cage inside a larger cage with a cat, was equivocal.
rats’ brains were dissected and measured for protein and catecholamine levels.** Anti-tumor activity.** Arachidonyl ethanolamide, in three cervical carcinoma (CxCa) cell lines at increasing doses with or without antagonists to receptors to arachidonyl ethanolamide, induced apoptosis of CxCa cell lines via aberrantly expressed vanilloid receptor-1. Arachidonyl ethanolamide-binding to the classical CB1 and CB2 cannabinoid receptors mediated a protective effect. A strong expression of the three forms of arachidonyl ethanolamide receptors was observed in ex vivo CxCa biopsies. Three cannabis constituents, CBD, Δ-8-THC, and cannabinol displayed anti-proliferative activity in several human cancer cell lines in vitro. They were oxidized to their respective paraquinones 2, 4, and 6. Quinone 2 significantly reduced cancer growth of HT-29 cancer in nude mice. Δ-9-THC binds and activates membrane receptors of the 7-transmembrane domain, G protein-coupled superfamily. Several putative endocannabinoids have been identified, including anandamide (AEA), 2-arachidonyl glycerol, and noladin ether. Synthesis of numerous cannabinomimetics has expanded the repertoire of cannabinoid receptor ligands with the pharmacodynamic properties of agonists, antagonists, and inverse agonists. These ligands have proven to be powerful tools both for the molecular characterization of cannabinoid receptors and the delineation of their intrinsic signaling pathways. Much of the understanding of the signaling mechanisms activated by cannabinoids has been derived from studies of receptors expressed by tumor cells. Cannabinoids and their derivatives exerted palliative effects in cancer patients by preventing nausea, vomiting, and pain and by stimulating appetite. These compounds have been shown to inhibit the growth of tumor cells in culture and animal models by modulating key cell-signaling pathways. Cannabinoids are usually well tolerated, and do not produce the generalized toxic effects of conventional chemotherapies.

**Anti-ulcer activity.** Petroleum ether extract of the dried aerial parts, administered intraperitoneally to male rats, was active. Antiviral activity. Hot water extract of the dried fruit, in vero cell culture at a concentration of 0.5 mg/mL, was inactive on herpes simplex 1 virus, measles virus, and poliovirus 1. Anxiolytic activity. AEA, a primary endogenous ligand of the brain cannabinoid receptors, is released in selected regions of the brain and is deactivated through a two-step process consisting of transport into cells followed by intracellular hydrolysis. Pharmacological blockade of the enzyme fatty acid amide hydrolase (FAAH), which is responsible for intracellular AEA degradation, produced anxiolytic-like effects in rats without causing the wide spectrum of behavioral responses typical of direct-acting cannabinoid agonists. These findings suggest that AEA contributes to the regulation of emotion and anxiety, and that FAAH might be the target for a novel class of anxiolytic drugs.

**Aphrodisiac activity.** The leaf, smoked by adults of both sexes, was active.

**Attention deficit hyperactivity disorder.** Attention deficit hyperactivity disorder has been considered a mental and behavioral disorder of childhood and adolescence. It is being increasingly recognized in adults, who may have psychiatric comorbidity with secondary depression, or a tendency to drug and alcohol abuse. A 32-year-old woman known for years as suffering from borderline personality disorder and drug dependence (including cannabis, LSD, and ecstasy) and alcohol abuse that did not respond to treatment was reported. Only when correctly diagnosed as attention deficit hyperactivity disorder and appropriately treated with the psychotropic stimulant methylphenidate...
(Ritalin®), was there significant improvement. She succeeded academically, which had not been possible previously, her craving for drugs diminished, and a drug-free state was reached.*46

**Auditory function.** Eight male subjects (aged 22–30 years) who had previously used cannabis were investigated. They performed air conduction pure tone audiometry in both ears over 0.5–8 kHz. A simple test of frequency selectivity by detecting a 4-kHz tone under two masking noise conditions was also carried out in one ear. Three test sessions at weekly intervals were carried out, at the start of which they ingested a capsule containing either placebo, 7.5, or 15 mg of THC. These were administered in a randomized cross-over, double-blind manner. Auditory testing was carried out 2 hours after ingestion. Blood samples were also obtained at this time point and assayed for ∆-9-THC and 11-hydroxy-THC levels. No significant changes in threshold or frequency resolution were seen with the dosages employed in this study.*367

**Barbiturate potentiation.** Flavonoid fraction of the leaf, administered intraperitoneally to mice, was active.*242 Petroleum ether extract of the dried entire plant, administered intraperitoneally to pigs at a dose of 250 mg/kg, was inactive.*302

**Behavioral effect.** A four-page, self-completed questionnaire was designed to determine the drugs used (licit, illicit, and doping substances) along with beliefs about doping and the psychosociological factors associated with their consumption. The questionnaire was distributed to high school students enrolled in a school sports association in eastern France. The completed forms were received from 1459 athletes: 4% stated that they had used doping agents at least once in their life (their main source of supply being peers and health professionals). Thirty-four percent of the sample smoked some tobacco, 66% used alcohol, 19% used cannabis, 4% took ecstasy, 10% took tranquilizers, 9% used hypnotics, 4% used creatine, and 41% used vitamins against fatigue. Beliefs about doping did not differ among doping agent users and nonusers, except for the associated health risks, which were minimized by users. Users of doping agents stated that the quality of the relations that they maintained with their parents was sharply degraded, and they reported that they were susceptible to influence and difficult to live with. More often than nondoping-agent users, these adolescents were neither healthy, although paradoxically, they seemed less anxious and were more self-confident.*302 Maternal exposure to ∆-9-THC in rats resulted in alteration in the pattern of ontogeny of spontaneous locomotor and exploratory behavior in the offspring. Adult animals exposed during gestational and lactational periods exhibited persistent alterations in the behavioral response to novelty, social interactions, sexual orientation, and sexual behavior. They also showed a lack of habituation and reactivity to different illumination conditions. Adult offspring of both sexes also displayed a characteristic increase in spontaneous and water-induced grooming behavior. Some of the effects were dependent on the sex of the animals being studied, and the dose of cannabinoid administered to the mother during gestational and lactational periods. Maternal exposure to low doses of THC sensitized the adult offspring of both sexes to the reinforcing effects of morphine, as measured in a conditioned place preference paradigm.*362

**β-Endorphin interaction.** ∆-9-THC administered to rats produced large increases in extracellular levels of β-endorphin in the ventral tegmental area and lesser increases in the shell of the nucleus accumbens (Nac). In rats that had learned to discriminate injections of THC from injections of vehicle, the opioid agonist
morphine did not produce THC-like discriminative effects, but markedly increased discrimination of THC. The opioid antagonist naloxone reduced the discriminative effects of THC. Bilateral microinjections of β-endorphin directly into the ventral tegmental area, but not into the shell of the Nac, markedly increased the discriminative effects of ineffective threshold doses of THC, but had no effect when given alone. The increase was blocked by naloxone.

**Binocular depth inversion reduction.** A study to assess whether the binocular depth inversion illusion (BDII) could detect subtle cognitive impairment owing to regular cannabis use was conducted. Ten regular cannabis users and 10 healthy controls from the same community sources, matched for age, sex, and premorbid intelligence quotient (IQ) were evaluated. The subjects were also compared on measures of executive functioning, memory, and personality. Regular cannabis users were found to have significantly higher BDII scores for inverted images. This was not to the result of a problem in the primary processing of visual information, as there was no significant difference between the groups for depth perception of normal images. There was no relationship between BDII scores for inverted images and time since the last dose, suggesting that the measured impairment of BDII more closely reflected chronic than acute effects of regular cannabis use. There were no significant differences between the groups for other neuropsychological measures of memory or executive function. A positive relationship was found between psychoticism as defined by the revised Eysenck Personality Questionnaire and cannabis, tobacco, and alcohol use. Cannabis users also used significantly larger amounts of alcohol. No relationship was found between BDII scores and drug use other than cannabis or psychoticism.

**Birth-weight effect.** A total of 32,483 cannabis-using women giving birth to live-born infants were investigated. The largest reduction in mean birth-weight for any cannabis use during pregnancy was 48 g (95% CI, 83–14 g), with considerable heterogeneity among the five studies. Mean birth-weight was increased by 62 g (95% CI, 8-g reduction – 132-g increase; p heterogeneity, 0.59) among infrequent users (≤ weekly), whereas cannabis use at least four times per week had a 131-g reduction in mean birth-weight (95% CI 52–209-g reduction; p heterogeneity, 0.25). From the five studies of low birth-weight, the pooled odds ratio for any use was 1.09 (95% CI 0.94–1.27; p heterogeneity, 0.19). In a cohort study consisted of a multiethnic population of 7470 pregnant women. Information on the use of drugs was obtained from personal interviews at entry to the study and assays of serum obtained during pregnancy. Pregnancy outcome data (low birth-weight [<2500 g], pre-term birth [<37 weeks gestation], and abruptio placentae) were obtained with a standardized study protocol. A total of 2.3% of the women used cocaine and 11% used cannabis during pregnancy. Cannabis use was not associated with low birth-weight (1.1, 0.9–1.5), pre-term birth (adjusted odds ratio [OR] 1.1, CI 0.8–1.3), or abruptio placenta (1.3, 0.6–2.8).

**Bladder dysfunction.** Two whole-plant extracts of Cannabis sativa were administered to patients with advanced multiple sclerosis (MS) and refractory troublesome lower urinary tract symptoms. The patients
took the extracts containing Δ-9-THC and CBD (2.5 mg of each per spray) for 8 weeks followed by THC-only (2.5 mg THC per spray) for a further eight weeks, and then into a long-term extension. Assessments included urinary frequency and volume charts, incontinence pad weights, cystometry, and visual analog scales for secondary troublesome symptoms. Twenty-one patients were recruited and data from 15 were evaluated. Urinary urgency, the number and volume of incontinence episodes, frequency, and nocturia all decreased significantly following treatment ($p < 0.05$, Wilcoxon’s signed rank test). Daily total voided, catheterized and urinary incontinence pad weights also decreased significantly for both extracts. Patient self-assessment of pain, spasticity, and quality of sleep improved significantly ($p < 0.05$, Wilcoxon’s signed rank test) with pain improvement continuing up to a median of 35 weeks. There were few troublesome side effects, suggesting that cannabis-based medicinal extracts are a safe and effective treatment for urinary and other problems in patients with advanced MS.

**Blood pressure stress reactivity effect.** Data from an ascorbic acid (AA) trial (Cetebe 3 g/day for 14 days, $n = 108$) were compared by substance use level regarding systolic blood pressure (SBP) stress reactivity to the anticipation and actual experience phases of a standardized psychological stressor (10 minutes of public speaking and arithmetic). Self-reported never users of cannabis, persons not currently smoking tobacco, and persons consuming three or more caffeine beverages daily all exhibited AA SBP stress reactivity protection to the actual stressor, but not during the anticipation phase. Self-reported ever cannabis users, current tobacco smokers, and persons consuming less than three caffeine beverages daily exhibited the AA SBP protection during the anticipation phase, but only the lower caffeine consumption group exhibited AA protection during both phases. Covariates (neuroticism, extraversion and depression scores, age, sex, body mass index) were not significant.

**Blood-borne sexually transmitted infections.** Substance use, including alcohol and illicit drugs, increases the risk for the acquisition and transmission of sexually transmitted infection (STI). The prevalence of blood-borne STI including human immunodeficiency virus (HIV), human T-cell lymphotrophic virus type 1, hepatitis B virus, and syphilis in residents of a detoxification and rehabilitation unit in Jamaica were investigated. The demographic characteristics and the results of laboratory investigations for STI in 301 substance abusers presented during a 5-year period were reviewed. The laboratory results were compared with those of 131 blood donors. The substances used by participants were alcohol, cannabis, and cocaine. None of the clients was an intravenous drug user. Female substance abusers were at higher risk for STI. The prevalence of STI in substance abusers did not differ significantly from that in blood donors (12% vs 10%). The prevalence of syphilis in substance abusers was significantly higher than that in blood donors (6% vs 3%, $p < 0.05$). The prevalence of syphilis was dramatically increased in female substance abusers and female blood donors (30%, $p < 0.001$ and 13%, $p < 0.05$, respectively). An excess of human T-cell lymphotrophic virus type 1 was also observed in female compared with male substance abusers. Unemployment was identified also as a risk factor for sexually transmitted disease in substance abusers.

**Brain aging effect.** The impact of duration of education, cannabis addiction and smoking on cognition and brain aging was studied in 211 healthy Egyptian volunteers with mean age of 46.4 ± 3.6 years (range, 20–76 years). The subjects were classified into two
groups: Gr I (n = 174; mean age, 49.9 ± 3.8 years; range, 20–76 years), nonaddicts, smokers, and nonsmokers, educated and noneducated, and Gr II cannabis addicts (n = 37; mean age, 43.6 ± 2.6 years; range, 20–72 years) all smokers, educated and noneducated. Outcome measures included the Paced Auditory Serial Addition test for testing attention and the Trailmaking test A and Trailmaking test B (TMb) for testing psychomotor performance. Age correlated positively with score of TMb in the nonaddict group and in the addict group (Trailmaking test A and TMb). Years of education correlated negatively with scores of TMb in the nonaddict group (Gr I) but not the addict group (Gr II). Cannabis addicts (Gr II) had significantly poorer attention than nonaddict normal volunteers (Gr I). It was determined that impairment of psychomotor performance is age related whether in normal nonaddicts or in cannabis addicts. A decline in attention was detected in cannabis addicts and has been considered a feature of pathological aging.

**Brain cannabinoid receptor.** In humans, psychoactive cannabinoids produce euphoria, enhancement of sensory perception, tachycardia, antinociception, difficulties in concentration, and impairment of memory. The cognitive deficiencies persist after withdrawal. The toxicity of cannabis has been underestimated for a long time, since recent findings revealed that Δ9-THC-induced cell death with shrinkage of neurons and DNA fragmentation in the hippocampus. The acute effects of cannabinoids, as well as the development of tolerance, are mediated by G protein-coupled cannabinoid receptors. The CB1 receptor and its splice variant, CB1A, are found predominantly in the brain with highest densities in the hippocampus, cerebellum, and striatum. The CB2 receptor is found predominantly in the spleen and in hemopoietic cells and has only 44% overall nucleotide sequence identity with the CB1 receptor. The existence of this receptor provided the molecular basis for the immunosuppressive actions of cannabis. The CB1 receptor mediates inhibition of adenylate cyclase, inhibition of N- and P/Q-type calcium channels, stimulation of potassium channels, and activation of mitogen-activated protein kinase. The CB2 receptor mediates inhibition of adenylate cyclase and activation of mitogen-activated protein kinase. The discovery of endogenous cannabinoid receptor ligands, AEA (N-arachidonylethanolamine), and 2-arachidonylglycerol made the notion of a central cannabinoid neuromodulatory system plausible. AEA is released from neurons on depolarization through a mechanism that requires calcium-dependent cleavage from a phospholipid precursor in neuronal membranes. The release of AEA is followed by rapid uptake into the plasma and hydrolysis by fatty-acid amidohydrolase. The psychoactive cannabinoids increase the activity of dopaminergic neurons in the ventral tegmental area–mesolimbic pathway. Because these dopaminergic circuits are known to play a pivotal role in mediating the reinforcing (rewarding) effects of the most drugs of abuse, the enhanced dopaminergic drive elicited by the cannabinoids is thought to underlie the reinforcing and abuse properties of cannabis. Thus, cannabinoids share a final common neuronal action with other major drugs of abuse such as morphine, ethanol, and nicotine in producing facilitation of the mesolimbic dopamine system. Hippocampal slices from humans, guinea pigs, rats, and mice, and cerebellar, cerebrocortical, and hypothalamic slices from guinea pigs were incubated with [3H] noradrenaline and then superfused. Tritium overflow was evoked either electrically (0.3 or 1 Hz) or by introduction of Ca2+ ions (1.3 µM) into Ca2+-free, K+-rich medium (25 µM) contain-
ing 1 µM of tetrodotoxin. The cyclic adenosine monophosphate (cAMP) accumulation stimulated by 10 µM of forskolin was determined in guinea pig hippocampal membranes. The following drugs were used: the cannabinoid receptor-agonists (-)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclo-hexanol (CP-55,940) and R(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-1-(1-naphthalenyl)methanone (WIN 55,212-2 [WIN]), the inactive S(-)-enantiomer of the latter (WIN 55,212-3) and the CB1 receptor antagonist N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazolecarboxamide (SR 141716). The electrically evoked tritium overflow from guinea pig hippocampal slices was reduced by WIN (peak inhibitory concentration 30%, 6.5) but not affected by WIN 55,212-3 up to 10 mM. The concentration–response curve of WIN was shifted to the right by SR 141716 (0.032-µM) (apparent pA2 8.2), which by itself did not affect the evoked overflow. WIN (1 µM) also inhibited the Ca\(^{2+}\)-evoked tritium overflow in guinea pig hippocampal slices and the electrically evoked overflow in guinea pig cerebellar, cerebrocortical, and hypothalamic slices, as well as in human hippocampal slices, but not in rat and mouse hippocampal slices. SR 141716 (0.32 µM) markedly attenuated the WIN-induced inhibition in guinea pig and human brain slices. SR 141716 (0.32 µM) by itself increased the electrically evoked tritium overflow in guinea pig hippocampal slices, but failed to do so in slices from the other brain regions of the guinea pig and in human hippocampal slices. The cAMP accumulation stimulated by forskolin was reduced by CP-55,940 and WIN. The concentration-response curve of CP-55,940 was shifted to the right by SR 141716 (0.1 µM; apparent pA2 8.3), that by itself did not affect cAMP accumulation. In conclusion, cannabinoid receptors of the CB1 subtype occur in the human hippocampus, where they may contribute to the psychotropic effects of cannabis, and in the guinea pig hippocampus, cerebellum, cerebral cortex, and hypothalamus. The CB1 receptor in the guinea pig hippocampus is located presynaptically, was activated by endogenous cannabinoids, and may be negatively coupled to adenylyl cyclase. The acute administration of AEA or THC in rats increased the maximum binding capacity (B\(_{\text{max}}\)) of cannabinoid receptors in the cerebellum and, particularly, in the hippocampus. This effect was also observed after 5 days of a daily exposure to AEA or THC. The increase in the B\(_{\text{max}}\) after the acute treatment seemed to be caused by changes in the receptor affinity (high K\(_{d}\)). The increase after the chronic exposure may be attributed to an increase in the density of receptors. The [\(^{3}H\)]CP-55,940 binding to cannabinoid receptors in the striatum, the limbic forebrain, the mesencephalon, and the medial basal hypothalamus was not altered after the acute exposure to AEA or THC. The chronic exposure to THC significantly decreased the B\(_{\text{max}}\) of these receptors in the striatum and nonsignificantly in the mesencephalon. This effect was not elicited after the chronic exposure to AEA and was not accompanied by changes in the K\(_{d}\). **Bronchoconstrictor activity.** Water extract of seed, administered by inhalation to human adults, was active. **Bronchodilator activity.** Petroleum ether extract of the aerial parts, administered orally to adults of both sexes, was inactive. **Cannabinoid hyperemesis.** Nineteen patients were identified with chronic cannabis abuse and a cyclical vomiting illness. Follow-up was provided with serial urine drug
screen analysis and regular clinical consultation to chart the clinical course. Of the 19 patients, five refused consent and were lost to follow-up, and five were excluded based on cofounders. In all cases, chronic cannabis abuse predated the onset of the cyclical vomiting illness. Cessation of cannabis abuse led to cessation of the cyclical vomiting illness in seven cases. Three cases did not abstain and continued to have recurrent episodes of vomiting. Three cases rechallenged themselves after a period of abstinence and suffered a return to illness. Two of these cases abstained again and became, and remain, well. The third case did not and remains ill. A novel finding was that 9 of the 10 patients, including the previously published case, displayed an abnormal washing behavior during episodes of active illness.

**Cannabinoid-induced Fos expression.** Cannabinoid CB1 receptor agonist CP-55,940 in Lewis and Wistar rats was investigated. A moderate (50 µg/kg) and a high (250 µg/kg) dose level were used. The 250-µg/kg dose caused locomotor suppression, hypothermia, and catalepsy in both strains, but with a significantly greater effect in Wistar rats. The 50-µg/kg dose provoked moderate hypothermia and locomotor suppression but in Wistar rats only. CP-55,940 caused significant Fos immunoreactivity in 24 out of 33 brain regions examined. The most dense expression was seen in the paraventricular nucleus of the hypothalamus, the islands of Calleja, the lateral septum (ventral), the central nucleus of the amygdala, the bed nucleus of the stria terminalis (lateral division), and the ventrolateral periaqueductal gray. Despite having a similar distribution of CP-55,940-induced Fos expression, Lewis rats showed less overall Fos expression than Wistar rats in nearly every brain region counted. This held equally true for anxiety-related brain structures (e.g., central nucleus of the amygdala, periaqueductal gray, and the paraventricular nucleus of the hypothalamus) and reward-related sites (Nac and pedunculopontine tegmental nucleus). In a further experiment, Wistar rats and Lewis rats did not differ in the amount of Fos immunoreactivity produced by cocaine (15 mg/kg). These results indicate that Lewis rats are less sensitive to the behavioral, physiological and neural effects of cannabinoids.

**Cannabis withdrawal effect.** A 35-year-old male was cognitively assessed prior to cessation of 18 years of daily cannabis use and monitored for several weeks post-cessation. Brain event-related potential measures of selective attention reflecting a difficulty in filtering out complex irrelevant information showed no indication of improvement over 6 weeks of abstinence. When tested in the acutely intoxicated state prior to cessation of use, a dramatic normalization of the event-related potential signature was observed. A treatment program based on supportive–expressive psychotherapy was administered and depression, anxiety, and general psychological health were monitored over the course of withdrawal from cannabis.

**Cannabis–amphetamine interaction.** Cannabinoid–amphetamine interactions were studied as follows:
1. 30 minutes after acute injection of (-)-∆-9-THC (0.1 or 6.4 mg/kg, intraperitoneally).
2. 30 minutes after the last injection of 14-daily treatment with (-)-∆-9-THC (0.1 or 6.4 mg/kg).
3. 24 hours after the last injection of 14-daily treatment with (-)-∆-9-THC (6.4 mg/kg).
Acute cannabinoid exposure antagonized the amphetamine-induced dose-dependent increase in locomotion, exploration, and the decrease in inactivity. Chronic treatment with (-)-∆-9-THC resulted in toler-
ance to this antagonistic effect on locomotion and inactivity but not on exploration, and potentiated amphetamine-induced stereotypes. Lastly, 24 hours of withdrawal after 14 days of cannabinoid treatment resulted in sensitization to the effects of D-amphetamine on locomotion, exploration, and stereotypes CS431.

Cannabis-induced coma. Two cases of cannabis-induced coma were reported following accidental ingestion of cannabis cookies. The possibility of cannabis ingestion should be considered in cases of unexplained coma in a previously healthy young child if signs of conjunctival hyperemia, pupillary dilatation, and tachycardia were present and other causes, such as central nervous system infection or trauma were unlikely CS458.

Cannabis-related arteritis. A 19-year-old man who presented with plantar claudication associated with necrosis in a toe underwent diagnostic arteriography and surgery for popliteal artery entrapment type III was studied. Surgical clearance resolved the popliteal artery entrapment but left the clinical symptoms unchanged. Closer questioning disclosed a history of cannabis consumption and intravenous vasodilatory therapy was started. After the 21-day course of vasodilator agents, the pain disappeared and the toe necrosis regressed. The patient stopped taking cannabis and had no signs of recurrence CS308. A 24-year-old woman who was a heavy cannabis smoker with progressive Raynauld’s phenomenon and digital necrosis, was investigated. Systemic sclerosis and other connective tissue disorders, as well as arteriosclerosis and arterial emboli were excluded with appropriate laboratory examinations. Arteriography revealed multiple forearms, palmar and digital occlusions with corkscrew-shaped vessels. Based on the characteristic arteriography and clinical findings, the diagnosis of cannabis arteritis was retained. With careful necrectomy, conservative wound dressings and secondary prostacyclin therapy a complete healing of digital necrosis was observed. There was no recurrence during the 6-month follow-up CS336. Young men were presented with distal arteriopathy of the lower limbs in three cases, and of the left upper limb in the remaining patient. Symptoms occurred progressively, distal pulses had disappeared, and distal necrosis was constant. Three patients suffered from Raynauld’s phenomenon, none of them presented with venous thrombosis. Radiological evaluation revealed distal abnormalities in all cases, and proximal arterial thrombosis in one case. The four patients were cannabis smokers for at least four years. With cannabis interruption and symptomatic treatment, lesions improved for three patients. For one of them, recurrence of arteriopathy occurred when he resumed smoking cannabis. For the fourth who never stopped cannabis, an amputation was necessary CS349. Ten male moderate tobacco smokers and regular cannabis users with a median age of 23.7 years, developed subacute distal ischemia of the lower or upper limbs, leading to necrosis in the toes and/or fingers and sometimes to distal limb gangrene. Two of the patients also presented with venous thrombosis and three patients were suffering from a recent Raynauld’s phenomenon. Biological test results did not show evidence of the classical vascular risk factors for thrombosis. Arteriographic evaluation in all of the cases revealed distal abnormalities in the arteries of feet, legs, forearms, and hands resembling those of Buerger’s disease. A collateral circulation sometimes with opacification of the vasa nervorum was noted. In some cases, arterial proximal atherosclerotic lesions and venous thrombosis were observed. Despite treatment with ilomedine and heparin in all cases, five amputations were necessary in four patients. The vasoconstrictor effect of cannabis on the vascular system has been
known for a long time. It has been shown that $\Delta^8$-THC and $\Delta^9$-THC may induce peripheral vasoconstrictor activity. Cannabis arteritis resembles Buerger’s disease, but patients were moderate tobacco smokers and regular cannabis users\textsuperscript{CS406}.

**Cannabis-related flashback.** A young man who offended a friend without any objective reason was reported. The report of the forensic psychiatrist demonstrated that the offense was committed under the influence of a cannabis flashback. The last time the offender had consumed cannabis was 2 weeks before the acts. A plasmatic detection was realized and showed a level of 6 ng/mL, 30 minutes after the beginning of the flashback\textsuperscript{CS383}.

**Capgras syndrome.** A report describes an apparently greater incidence of Capgras syndrome among the Maori population compared with the European population. Five cases of Capgras syndrome were identified in the eastern catchment area where 19% of the population identified as Maori, 75% as European, and 6% as other or nonspecified. All of the cases occurred in Maori patients. No cases were identified in the western catchment area where 12% of the population identified as Maori, 87% as European, and 1% as other or nonspecified. Four of five cases were females. Two cases had a history of cannabis use. Three cases had exhibited dangerous behavior towards family members\textsuperscript{CS410}.

**Carcinogenic activity.** The dried leaf, administered intraperitoneally to rats of both sexes at a dose of 7 mg/kg/week, was active. The animals were irradiated with $\gamma$ radiation between 40 and 50 days of age and observed for 78 weeks. There was a greater incidence of tumors in animals given marijuana extract and $\gamma$ radiation than either marihuana or $\gamma$ radiation alone\textsuperscript{CS223}.

**Cardiorespiratory effect.** Fifty stable patients (25 males, 25 females) with methadone maintenance treatment (MMT) programs were investigated. Forty-six MMT patients were current tobacco smokers, 19 were current cannabis users, and none were currently using opioids other than prescribed methadone. Abnormalities of respiratory function were defined as those results outside the 95% confidence interval of reference values for normal subjects adjusted for age, weight, height, and sex. Thirty-one (62%) MMT patients had reduced carbon monoxide transfer factor; 17 (34%) had lowered single breath alveolar volume, and 43 (86%) had a reduced carbon monoxide transfer factor–alveolar volume ratio. Six patients (12%) had reduced forced expiratory volume in 1 second (FEV1); one (2%) had reduced forced vital capacity (FVC); and nine (18%) had an obstructive ventilatory defect. Ten (20%) patients had arterial CO, pressure higher than 45 mmHg and 14 (28%) had alveolar to arterial oxygen gradient higher than 15 mmHg. Chest X-ray, echocardiography, and electrocardiogram showed no significant abnormalities\textsuperscript{CS256}.

The potent cannabinoid receptor agonists WIN55,212-2 (0.05, 0.5, or 5 pmol/50 nL) and HU-210 (0.5 pmol/50 nL) or the CB1 receptor antagonist/inverse agonist AM281 (1 pmol/100 nL) were microinjected into the rostral ventrolateral medulla oblongata (RVLM) of urethane-anesthetized, immobilized and mechanically ventilated male Sprague–Dawley rats ($n = 22$). Changes in splanchnic nerve activity, phrenic nerve activity, mean arterial pressure, and heart rate in response to cannabinoid administration were recorded. The CB1 receptor gene was expressed throughout the ventrolateral medulla oblongata. Unilateral microinjection of WIN 55,212-2 into the RVLM evoked short-latency, dose-dependent increases in splanchnic nerve activity (0.5 pmol; 175 ± 8%, $n = 5$) and mean arterial pressure (0.5 pmol; 26 ± 3%, $n = 8$), and abolished phrenic nerve activity (0.5 pmol; duration of apnea: 5.4 ± 0.4 seconds, $n = 8$), with little change in heart rate ($p < 0.005$). HU-210, structurally related to $\Delta^9$-THC,
evoked similar effects when microinjected into the RVLM (n = 4). Prior microinjection of AM281 produced agonist-like effects, and significantly attenuated the response to subsequent injection of WIN (0.5 pmol, n = 4).**

**Cardiovascular effects.** The leaf, smoked by adults of both sexes, at a dose of 600 mg/person (1–1.5% THC), produced no adverse effects on blood pressure, electrocardiogram, and the heart. Cannabis and Δ-9-THC increase heart rate, slightly increase supine blood pressure, and on occasion produced marked orthostatic hypotension. Cardiovascular effects in animals are different, with bradycardia and hypotension the most typical responses. Cardiac output increases, and peripheral vascular resistance and maximum exercise performance decrease. Tolerance to most of the initial cardiovascular effects appears rapidly. With repeated exposure, supine blood pressure decreases slightly, orthostatic hypotension disappears, blood volume increases, heart rate slows, and circulatory responses to exercise and Valsalva maneuver are diminished, consistent with centrally mediated, reduced sympathetic, and enhanced parasympathetic activity. Receptor-mediated and probably nonneuronal sites of action account for cannabinoid effects. The endocannabinoid system appears important in the modulation of many vascular functions. Cannabis’ cardiovascular effects are not associated with serious health problems for most young, healthy users, although occasional myocardial infarction, stroke, and other adverse cardiovascular events are reported.

**Cataleptic effect.** Petroleum ether extract of the dried entire plant, administered intraperitoneally to guinea pigs at a dose of 100 mg/kg, was active.

**CB1 cannabinoid receptor in human placenta.** CB1 (G protein-coupled) receptor and FAAH expression in human term placenta were investigated by immunohistochemistry. CB1 receptor was found in all layers of the membrane, with particularly strong expression in the amniotic epithelium and reticular cells and cells of the maternal decidua layer. Moderate expression was observed in the chorionic cytotrophoblasts. The expression of FAAH was highest in the amniotic epithelial cells, chorionic cytotrophoblast, and maternal decidua layer. The results suggest that the human placenta is a likely target for cannabinoid action and metabolism. This is consistent with a placental site of action of endocannabinoids and cannabis being responsible, at least in part, for the poor outcomes associated with cannabis consumption and pathology in the endocannabinoid system during pregnancy.

**Central nervous system depressant activity.** Fluidextract of the aerial parts, administered intraperitoneally to rats at a dose of 25 mg/kg, was active. The fluidextract, administered orally to dogs, produced ataxia. The leaf, smoked by human adults, produced a decrease in psychomotor performance.

**Central nervous system effect.** Δ-9-THC activates the two G protein-coupled receptors CB1 and CB2. The endogenous ligands of these receptors were identified as lipid metabolites of arachidonic acid, named endocannabinoids. The two most studied endocannabinoids are AEA and 2-arachidonyl-glycerol. The CB1 receptor is massively expressed throughout the central nervous system, whereas CB2 expression seems restricted to immune cells. Following endocannabinoid binding, CB1 receptors modulate second messenger cascades (inhibition of adenylate cyclase, activation of mitogen-activated protein kinases and of focal-adhesion kinases), as well as ionic conductances (inhibition of voltage-dependent calcium channels, activation of several potassium channels). Endocannabinoids transiently silenced synapses by decreasing neurotransmitter release. They play major roles in various forms of synaptic plasticity.
because of their ability to behave as retrograde messengers and activate noncannabinoid receptors (such as vanilloid receptor type-1). Mice strain with a disrupted CB1 gene (CB1 knockout mice) appeared healthy and fertile, but they had a significantly increased mortality rate. They also displayed reduced locomotor activity, increased ring catalepsy, and hypalgesia in hotplate and formalin tests. Δ9-THC-induced ring catalepsy, hypomobility, and hypothermia were completely absent in CB1 mutant mice. In contrast, Δ9-THC-induced analgesia in the tail-flick test and other behavioral (licking of the abdomen) and physiological (diarrhea) responses after Δ9-THC administration were found. Results indicate that most, but not all, central nervous system effects of Δ9-THC are mediated by the CB1 receptor.

Central nervous system stimulant activity. The resin, ingested by a 4-year-old girl, showed signs of stupor alternating with brief intervals of excitation and foolish laughing with atactic movements. Her temperature, blood pressure, pulse, hemoglobin, leukocytes, serum electrolytes, and serum urea were normal. Respiratory rate was 12 beats per minute. Blood sugar elevated. Recovery was complete within 24 hours with no treatment.

Cerebellar clock-altering effect. Twelve volunteers who smoked cannabis recreationally about once weekly, and 12 volunteers who smoked daily for a number of years performed a self-paced counting task during positron emission tomography imaging, before and after smoking cannabis and placebo cigarettes. Smoking cannabis increased regional cerebral blood flow in the ventral forebrain and cerebellar cortex in both groups, but resulted in significantly less frontal lobe activation in chronic users. Counting rate increased after smoking cannabis in both groups, as did a behavioral measure of self-paced tapping, and both increases correlated with regional cerebral blood flow in the cerebellum. Results indicate that smoking cannabis appears to accelerate a cerebellar clock-altering self-paced behaviors.

Clinical endocannabinoid deficiency. Clinical endocannabinoid deficiency, and the prospect that it could underlie the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome, and other functional conditions alleviated by clinical cannabis were studied. Migraine has numerous relationships to endocannabinoid function. AEA potentiated 5-hydroxytryptamine (HT1A) and inhibited 5-HT2A receptors supporting therapeutic efficacy in acute and preventive migraine treatment. Cannabinoids also demonstrated dopamine-blocking and anti-inflammatory effects. AEA is tonically active in the periaqueductal gray matter, a migraine generator. THC modulated glutamatergic neurotransmission via N-methyl-D-aspartic acid-receptors. Fibromyalgia is now conceived as a central sensitization state with secondary hyperalgesia. Cannabinoids have similarly demonstrated the ability to block spinal, peripheral and gastrointestinal mechanisms that promote pain in headache, fibromyalgia, irritable bowel syndrome and related disorders.

Cognitive functioning. Cognitive performance was examined in 145 adolescents aged 13–16 years for whom prenatal exposure to cannabis and cigarettes had been ascertained. The subjects were from a low-risk, predominantly middle-class sample participating in an ongoing, longitudinal study. The assessment battery included tests of general intelligence, achievement, memory, and aspects of executive functioning. Consistent with results obtained at earlier ages, the strongest relationship between prenatal maternal cigarette smoking and cognitive variables was seen with overall intelligence and aspects of auditory functioning, whereas prenatal exposure to mari-
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juan was negatively associated with tasks that required visual memory, analysis, and integration. A multisite, retrospective, cross-sectional, neuropsychological study was conducted among 102 near-daily cannabis users (51 long-term users: mean, 23.9 years of use; 51 shorter-term users: mean, 10.2 years of use), compared with 33 non-user controls. Measures from nine standard neuropsychological tests that assessed attention, memory, and executive functioning were administered prior to entry into a treatment program following a median 17-hour abstinence. Long-term cannabis users performed significantly less well than shorter-term users and controls on tests of memory and attention. On the Rey Auditory Verbal Learning Test, long-term users recalled significantly fewer words than either shorter-term users ($p = 0.001$) or controls ($p = 0.005$). There was no difference between shorter-term users and controls. Long-term users showed impaired learning ($p = 0.007$), retention ($p = 0.003$), and retrieval ($p = 0.002$) compared with controls. Both user groups performed poorly on a time estimation task ($p < 0.001$ vs controls). Performance measures often correlated significantly with the duration of cannabis use, being worse with increasing years of use, but were unrelated to withdrawal symptoms and persisted after controlling for recent cannabis use and other drug use. A patient with a history of traumatic brain injury along with current mood disorder and cannabis use was reported. The impact of cannabis use appeared to have a detrimental effect on his mood. Treatment of the mood disorder resulted in larger cognitive gains. Sixty healthy volunteers (a negative urine drug-screening test was prerequisite) were investigated. On the first day, baseline data were obtained from a physical examination and a psychological test battery for the investigation of visual and verbal memory and cognitive perceptual performance. On the second day, subjects received a regular cigarette or one containing 290 mg/kg body weight of THC. Physical and psychological assessments were performed immediately (15 minutes) after subjects smoked their cigarettes. Twenty-four hours later, physical and psychological examinations were repeated. Results suggest that perceptual motor speed and accuracy, two very important parameters of driving ability, seem to be impaired immediately after cannabis consumption. The analyses included 1318 participants under age 65 years who completed the Mini-Mental State Examination (MMSE) during three study waves in 1981, 1982, and 1993–1996. Individual MMSE score differences between waves two and three were calculated for each study participant. After 12 years, study participants’ scores declined a mean of 1.20 points on the MMSE (standard deviation, 1.90), with 66% having scores that declined by at least one point. Significant numbers of scores declined by three points or more (15% of participants in the 18–29-year-old age group). There were no significant differences in cognitive decline between heavy users, light users, and nonusers of cannabis. There were also no male–female differences in cognitive decline in relation to cannabis use. From 250 individuals consuming cannabis regularly, 99 healthy, free of any other past or present drug abuse, or history of neuropsychiatric disease cannabis users were selected. After an interview, physical examination, analysis of routine laboratory parameters, plasma/urine analyses for drugs, and Minnesota Multiphasic Personality Inventory testing, users and respective controls were subjected to a computer-assisted attention test battery comprising visual scanning, alertness, divided attention, flexibility, and working memory. Of the potential predictors of test performance within the user group, including present age, age of onset of cannabis use, degree of acute
intoxication (THC + THC–OH plasma levels), and cumulative toxicity (estimated total life dose), an early age of onset turned out to be the only predictor, predicting impaired reaction times exclusively in visual scanning. Early-onset users (onset before age 16; \( n = 48 \)) showed a significant impairment in reaction times in this function, whereas late-onset users (onset after age 16; \( n = 51 \)) did not differ from controls (\( n = 49 \)). Male volunteers (\( n = 5 \)) with histories of moderate alcohol and cannabis use were administered three doses of alcohol (0.25, 0.5, or 1 g/kg), three doses of cannabis (4.8, or 16 puffs of 3.55% ∆9-THC), and placebo in random order under double blind conditions in seven separate sessions. Blood alcohol concentration (10–90 mg/dL) and THC levels (63–188 ng/mL) indicated that active drug was delivered to subjects dose dependently. Alcohol and cannabis produced dose-related changes in subjective measures of drug effect. Ratings of perceived impairment were identical for the high doses of alcohol and cannabis. Both drugs produced comparable impairment in digit–symbol substitution and word recall tests, but had no effect in time perception and reaction time tests. Alcohol, but not cannabis, slightly impaired performance in a number recognition test\(^{3446}\).

**Comorbid dysthymia and substance disorder.** A total of 642 patients were assessed. Thirty-nine had substance-related disorder and dysthymia (SRD-dysthymia) and 308 had SRD only. Data on past use were collected by a research associate using a questionnaire. The patients with SRD-dysthymia and SRD did not differ with regard to use of alcohol, tobacco, and benzodiazepines. The patients with SRD-dysthymia started caffeine use at an earlier age, had shorter “use careers” of cocaine, amphetamines, and opiates, and had fewer days of cocaine and cannabis use in the last year. They also had a lower rate of cannabis abuse/dependence. The results indicated that patients with dysthymia and SRD have exposure to most substances of abuse that was comparable to patients with SRD only. They selectively use certain substances less often than patients with SRD only\(^{3443}\). A course and severity of SRD among 642 patients with comorbid major depressive disorder (MDD) was analyzed by means of both retrospective and concurrent data. Data on course included lifetime use, age at first use, years of use, use in the last year, periods of abstinence, and current diagnosis. Data on severity included two measures of SRD-associated problems, substance abuse vs dependence, self-help activities, and number of substances being abused. SRD-MDD patients tended to manifest lower levels of cannabis, opiate, and cocaine use, and more SRD-only patients were abusing three or more substances. Men with SRD-MDD demonstrated longer mean durations of abstinence compared with men with SRD-only, whereas SRD-MDD women demonstrated shorter mean durations of abstinence, compared with women with SRD-only. MDD-SRD patients showed slightly less substance abuse, but SRD severity was comparable with SRD-only patients\(^{3441}\).

**Covariation among risk behaviors.** A sample of 913 sexually active high school students completed a self-administered questionnaire that required mainly “yes” or “no” answers to questions involving participation in a range of risk behaviors. Contraceptive nonuse was not significantly associated with use of cigarettes, alcohol, or inhalants; perpetration or being a victim of violence; exposure to risk of physical injury; and suicidality. For males only, there was a significant inverse association between contraceptive nonuse and use of cannabis in the previous month. This was not the case for lifetime cannabis use for either gender\(^{3404}\).
**Cyclo-oxygenase inhibition.** Ethanol (100%) extract and essential oil of the aerial parts were active, IC$_{50}$ 6.7 mg/L and 7.5 mg/L, respectively.$^{59}$

**Cytochrome P450 and 2C6 expression.** Hashish (cannabis) and heroin effect on the expression of cytochrome P450 2E1 (CYP 2E1) and cytochrome P450 2C6 (CYP 2C6) was measured after single (24 hours) and repeated-dose treatments (four consecutive days). The expression of CYP 2E1 was slightly induced after single-dose treatments and markedly induced after repeated-dose treatments of mice with hashish (10 mg/kg body weight). It is believed that N-nitrosamines are activated principally by CYP 2E1 and the activity of N-nitrosodimethylamine was found to be increased after single- and repeated-dose treatments of mice with hashish by 23 and 41%, respectively. Hashish treatments of mice increased the total hepatic content of CYP by 112 and 206%, respectively; aryl hydrocarbon hydroxylase activity by 110 and 165%, respectively; nicotinamide adenine dinucleotide phosphate–cytochrome c reductase activity by 21 and 98%, respectively, and glutathione level by 81 and 173%, respectively. The level of free radicals (thiobarbituric acid-reactive substances) was potentially decreased after single- or repeated-dose treatments with either hashish or heroin.$^{53}$

**Cytotoxic activity.** Ethanol (50%) extract of the entire plant, in cell culture, was inactive on CA-9KB, ED$_{50}$ greater than 20 µg/mL.$^{50}$ Water extract of the dried seed, in cell culture at a concentration of 500 µg/mL, was inactive on CA-mammary-microalveolar.$^{54}$

**Cytotoxic effect.** THC, in leukemic cell lines (CEM, HEL-92, and HL60) and in peripheral blood mononuclear cells, 6 hours after exposure induced apoptosis, even at one times the IC$_{50}$. THC did not appear to act synergistically with cytotoxic agents, such as cisplatin. THC-induced cell death was preceded by significant changes in the expression of genes involved in the mitogen-activated protein kinase signal transduction pathways. Both apoptosis and gene expression changes were altered independent of p53 and the cannabinoid 1 and 2 receptors (CB1-R and CB2-R).$^{55}$

**Depressant activity.** Heavy cannabis use and depression are associated and evidence from longitudinal studies suggests that heavy cannabis use may increase depressive symptoms among some users.$^{56}$ Participants (n = 1920) were reassessed as part of a follow-up study. The analysis focused on two cohorts: those who reported no depressive symptoms at baseline (n = 849) and those with no diagnosis of cannabis abuse at baseline (n = 1,837). Symptoms of depression, cannabis abuse, and other psychiatric disorders were assessed with the Diagnostic Interview Schedule. In participants with no baseline depressive symptoms, those with a diagnosis of cannabis abuse at baseline were four times more likely than those with no cannabis abuse diagnosis to have depressive symptoms at the follow-up assessment, after adjusting for age, gender, antisocial symptoms, and other baseline covariates. These participants were more likely to have experienced suicidal ideation and anhedonia during the follow-up period. Among the participants who had no diagnosis of cannabis abuse at baseline, depressive symptoms at baseline failed to significantly predict cannabis abuse at the follow-up assessment.$^{57}$ The relationship between depressive symptoms and polydrug use (alcohol, cannabis, and cocaine) among blacks in a high-risk community was studied. A street sample (n = 570) from four high-risk communities was collected through personal interviews. Interviewers asked respondents about their drug use behavior during the past 30 days and their depressive symptoms during the past week.
Odds ratios and logistic regressions, adjusted for age and sex, were used to assess the relationship between depressive symptoms and drug and polydrug use (drug use involving cocaine). Results showed that depressive symptoms are significantly associated with polydrug use. Depressive symptoms were not associated with alcohol use or with the combination of alcohol and cannabis use.  

**Diabetic ketoacidosis.** One hundred fifty-eight young adults, aged 16–30 years, with type 1 diabetes, attending an urban diabetes clinic, were sent an anonymous confidential postal questionnaire to determine the prevalence of street drug use. Eighty-five completed responses were received. Twenty-nine percent of respondents admitted to using street drugs. Of those, 68% habitually took street drugs more than once a month. Seventy-two percent of users were unaware of the adverse effects on diabetes. Results indicated that the street drug usage in young adults with type 1 diabetes is common and may contribute to poor glycemic control and serious complications of diabetes.  

**Digital necrosis.** An 18-year-old woman, with a history of severe anorexia nervosa of 5 years’ duration, who acknowledged regular use of tobacco and cannabis, was hospitalized for necrosis of the left index and thumb that had occurred shortly after left radial artery puncture for blood gas analysis. Acrocyanosis of the four limbs had been present since the onset of anorexia nervosa. Arteriography of the upper limbs showed major spasm of the left radial and cubital arteries and thromboses in the left interdigital arteries of the left index and thumb. The distal portions of the arteries were then on the left and on the right. The necrotic lesions healed after intravenous administration of ilomedine and interruption of tobacco and cannabis. Acrocyanosis of the four limbs persisted.  

**Discriminative stimulus effect.** Rhesus monkeys, trained to discriminate ∆9-THC from vehicle in a two-lever drug discrimination procedure, were tested with a variety of psychoactive drugs, including cannabinoids or drugs from other classes. The results indicated that ∆9-THC discrimination showed pharmacological specificity, in that none of the noncannabinoid drugs fully substituted for ∆9-THC. The classical cannabinoids, ∆9-THC and ∆8-THC, and the novel cannabinoids, WIN and 1-butyl-2-methyl-3-(1-naphthoyl)indole, produced full dose-dependent substitution for ∆9-THC in all monkeys. A heptyl indole derivative failed to substitute for ∆9-THC, but it also did not displace [3H] CP-55,940 from its binding site.  

**DNA synthesis inhibition.** Ethanol (95%) extract of the dried resin, administered intraperitoneally to toads at a dose of 10 mg/day for 14 days, was active. The results were significant at p < 0.01 level.  

**Dopamine metabolism.** The effect of repeated administrations of THC or WIN, a synthetic cannabinoid receptor agonist, on dopamine turnover in the prefrontal cortex, striatum, and Nac in rats, was investigated. THC or WIN (twice daily for seven or 14 days) caused a persistent and selective reduction in medial prefrontal cortical dopamine turnover. No significant alterations of dopamine metabolism were observed in the Nac or striatum. These dopaminergic deficits in the prefrontal cortex were observed after a drug-free period of up to 14 days. The cognitive dysfunction produced by heavy, long-term cannabis use may be conserved, in part, by drug-induced alterations in frontal cortical dopamine turnover. Two weeks’ administration of THC to rats, reduced dopamine transmission in the medial prefrontal cortex, whereas dopamine metabolism in striatal regions was unaffected.
Dopamine release. A 38-year-old drug-free schizophrenic patient took part in a single photon emission computerized tomographic study of the brain, and smoked cannabis secretively during a pause in the course of an imaging session. Cannabis had an immediate calming effect, followed by a worsening of psychotic symptoms a few hours later. A comparison of the two sets of images, obtained before and immediately after smoking cannabis, indicated a 20% decrease in the striatal dopamine D2 receptor-binding ratio, suggestive of increased synaptic dopaminergic activity.

Dopamine transmission modulation. The endogenous cannabinoid system is a new signaling system composed by the central (CB1) and the peripheral (CB2) receptors, and several lipid transmitters including AEA and 2-arachidonylglycerol. Cannabinoid CB1 receptors are present in dopamine projecting brain areas. In primates and certain rat strains it is also located in dopamine cells of the A8, A9, and A10 mesencephalic cell groups, as well as in hypothalamic dopaminergic neurons controlling prolactin secretion. CB1 receptors co-localize with dopamine D1/D2 receptors in dopamine projecting fields. Manipulation of dopaminergic transmission is able to alter the synthesis and release of AEA, as well as the expression of CB1 receptors. CB1 receptors can switch their transduction mechanism to oppose to the ongoing dopamine signaling. Acute blockade of CB1 receptor potentiates the facilitatory role of dopamine D2 receptor agonists on movement. CB1 stimulation results in sensitization to the motor effects of indirect dopaminergic agonists.

Dyskinetic activity. A 4-week dose escalation study was performed to assess the safety and tolerability of cannabis in six patients with Parkinson’s disease (PD) with levodopa (L-DOPA)-induced dyskinesia. Then a randomized, placebo-controlled crossover study was performed, in which 19 patients with PD were randomized to receive oral cannabis extract followed by placebo or vice versa. Each treatment phase lasted for 4 weeks with an intervening 2-week washout phase. The primary outcome measure was a change in Unified Parkinson’s Disease Rating Scale (UPDRS) (items 32 to 34) dyskinesia score. Secondary outcome measures included the Rush scale, Bain scale, tablet arm drawing task, and total UPDRS score following a levodopa challenge, as well as patient-completed measures of a dyskinesia activities of daily living scale, the PDQ-39, on-off diaries, and a range of category rating scales. Seventeen patients completed the study. Cannabis was well tolerated and had no pro- or anti-parkinsonian action. There was no evidence for a treatment effect on L-DOPA-induced dyskinesia as assessed by the UPDRS, or any of the secondary outcome measures. An anonymous questionnaire sent to all patients attending the Prague Movement Disorder Center revealed that 25% of 339 respondents had taken cannabis and 45.9% of these described some form of benefit. 2,4,5-Trihydroxyphenethylamine (6-hydroxydopamine)-lesioned rats were treated with the enantiomers of the synthetic cannabinoid 7-hydroxy-Δ6-THC 1,1-dimethylheptyl. Treatment with its (-) (3R, 4R) enantiomer (code name HU-210), a potent cannabinoid receptor type 1 agonist, reduced the rotations induced by L-DOPA/carbidopa or apomorphine by 34 and 44%, respectively. Treatment with the (+) (3S, 4S) enantiomer (code name HU-211), an N-methyl-D-aspartate antagonist, and the psychotropically inactive cannabis constituent: CBD and its primary metabolite, 7-hydroxy-cannabinol, did not show any reduction of rotational behavior. The results indicate that activation of the
CB1 stimulates the dopaminergic system ipsilaterally to the lesion, and may have implications in the treatment of PD.\textsuperscript{338}  

**Dystonic activity.** The neural mechanisms underlying dystonia involve abnormalities within the basal ganglia—in particular, overactivity of the lateral globus pallidus. Cannabinoid receptors are located presynaptically on γ-aminobutyric acid receptor (GABA) terminals within the globus pallidus internus, where their activation reduces GABA reuptake. Cannabinoid receptor stimulation may thus reduce overactivity of the globus pallidus, and thereby reduce dystonia. A double-blind, randomized, placebo-controlled, crossover study using the synthetic cannabinoid receptor agonist nabilone in patients with generalized and segmental primary dystonia showed no significant reduction in dystonia following treatment with nabilone.\textsuperscript{390}  

**Embryotoxic effect.** Resin, administered orally to pregnant rabbits at a dose of 1 mL/kg, was active.\textsuperscript{167}  

**Endocrine effect.** Animal models have demonstrated that cannabinoid administration acutely altered multiple hormonal systems, including the suppression of the gonadal steroids, growth hormone, prolactin, and thyroid hormone and the activation of the hypothalamic–pituitary–adrenal (HPA) axis. These effects were mediated by binding to the endogenous cannabinoid receptor in or near the hypothalamus. Despite these findings in animals, the effects in humans have been inconsistent, and discrepancies were likely owing in part to the development of tolerance.\textsuperscript{363} Intravenous administration of three cannabinoid agonists (AEA, methanandamide, and WIN) to nine castrated male calves under stress-free conditions provoked immediate increases of serum cortisol and respiration rate, and produced rapid hypoalgesia to cutaneous pain and thermal stimuli. AEA and methanandamide did not affect serum prolactin. Administration of WIN increased serum prolactin abruptly. None of the cannabinoid receptor agonists affected serum growth hormone.\textsuperscript{420}  

**Environmental stress and cannabinoids interaction.** Anxiety and panic are the most common adverse effects of cannabis intoxication. Data suggest that cannabinoid CB1 receptor modulation of amygdalar activity contributes to these phenomena. Using Fos as a marker, it was tested the hypothesis that environmental stress and CB1 cannabinoid receptor activity interact in the regulation of amygdalar activation in male mice. Both 30 minutes of restraint and CB1 receptor agonist treatment (Δ-9-THC [2.5 mg/kg]) or CP-55,940 (0.3 mg/kg); by intraperitoneal injection) produced barely detectable increases in Fos expression within the central amygdala (CeA). The combination of restraint and CB1 agonist administration produced robust Fos induction within the CeA, indicating a synergistic interaction between environmental stress and CB1 receptor activation. An inhibitor of endocannabinoid transport, AM404 (10 mg/kg), produced an additive interaction with restraint within the CeA. In contrast, FAAH inhibitor-treated mice (URB597, 1 mg/kg) and FAAH (−/−) mice did not exhibit any differences in amygdalar activation in response to restraint compared with control mice. In the basolateral amygdala (BLA) and medial amygdala, restraint stress produced a low level of Fos induction, which was unaffected by cannabinoid treatment. The CB1 receptor antagonist SR141716 dose-dependently increased Fos expression in the BLA and CeA.\textsuperscript{272}  

**Epileptic effect.** Δ-9-THC at a dose of 1 µM, significantly depressed evoked depolarizing postsynaptic potentials (PSPs) in rat olfactory cortex neurones. A standardized cannabis extract (SCE) and Δ-9-THC-free SCE significantly potentiated evoked PSPs (all results were fully reversed by the CB1 receptor antagonist SR141716A, 1 µM). The potentiation by Δ-9-THC-free SCE
was greater than that produced by SCE. On comparing the effects of Δ-9-THC-free SCE on evoked PSPs and artificial PSPs (aPSPs; evoked electrotonically following brief intracellular current injection), PSPs were enhanced, whereas aPSPs were unaffected, suggesting that the effect was not resulting from changes in background input resistance. Similar recordings made using CB1 receptor-deficient knockout mice and wild-type littermate controls revealed cannabinoid or extract-induced changes in membrane resistance, cell excitability and synaptic transmission in wild-type mice that were similar to those seen in rat neurones, but no effect on these properties were seen in CB1 receptor-deficient knockout mice cells. Results indicated that the unknown extract constituent(s) effects over-rode the suppressive effects of Δ-9-THC on excitatory neurotransmitter release, which may explain some patients’ preference for herbal cannabis rather than isolated Δ-9-THC (owing to attenuation of some of the central Δ-9-THC side effects) and possibly account for the rare incidence of seizures in some individuals taking cannabis recreationally. A SCE with pure Δ-9-THC, at matched concentrations of Δ-9-THC, and a Δ-9-THC-free extract (Δ-9-THC-free SCE) in in vitro rat brain slice model of epilepsy were examined. In the in vitro epilepsy model, in which sustained epileptiform seizures were induced by the muscarinic receptor agonist oxotremorine-M in immature rat piriform cortical brain slices, SCE was a more potent and again more rapidly-acting anticonvulsant than isolated Δ-9-THC. Δ-9-THC-free extract also exhibited anticonvulsant activity. CBD did not inhibit seizures, nor did it modulate the activity of Δ-9-THC in this model. These results demonstrated that not all of the therapeutic actions of cannabis herb might be a result of the Δ-9-THC content.

**Estrogen receptors stimulating effect.** THC, CBD, and desacetyllevonantradol, in estrogen-induced MCF-7 breast cancer cells at concentrations of no more than 10 µM, produced no effect. THC failed to antagonize the response to estradiol under conditions in which the antiestrogen LY156758 (keoxifene; raloxifene) was effective. The phytoestrogen formononetin behaved as an estrogen at high concentrations, and this response was antagonized by LY156758. THC, desacetyllevonantradol, or CBD did not stimulate transcription of an EREtkCAT reporter gene transiently transfected into MCF-7 cells.

**Estrogenic effect.** Petroleum ether extract of the resin was active on the rat non-pregnant uterus. Resin, in the ration of immature and ovariecotomized rats at a concentration equivalent to 250 ppm THC/animal, was inactive. Petroleum ether extract of the dried aerial parts, administered intraperitoneally to mice and rats at doses of 1 and 5 mg/animal, respectively, for 64 days, was active. Petroleum ether extract of the dried aerial, administered intraperitoneally to female rats, produced weak activity. Petroleum ether extract of the aerial parts, administered intraperitoneally to female rats, produced weak activity. Petroleum ether extract of the entire plant, administered by gastric intubation to rats at a dose of 75 mg/kg for 70 days, was active.

**Estrous cycle disruption effect.** Ethanol (95%) extract of the dried aerial parts, administered intraperitoneally to gerbils at a dose of 2.5 mg/animal daily for 60 days, was active. Petroleum ether extract of the dried aerial, administered intraperitoneally to mice and rats at doses of 1 and 5 mg/animal, respectively, for 64 days, was active. Petroleum ether extract of the dried aerial, administered intraperitoneally to female rats, produced weak activity. Petroleum ether extract of the entire plant, administered by gastric intubation to female mice at doses of 75 mg/kg and 150 mg/kg, was active. A dose of 3 mg/kg produced weak activity. Petroleum ether extract of the resin, administered intraperitoneally to female rats at doses of 10 and 20 mg/kg, was active. Resin, administered orally to female rats at doses of 3, 15, and 75 mg/kg daily for 72 days, was active.

**Familial Mediterranean fever.** A patient with familial Mediterranean fever was presented with chronic relapsing pain and
inflammation of gastrointestinal origin. After determining a suitable analgesic dosage, a double-blind, placebo-controlled, crossover trial was conducted using 50 mg of Δ-9-THC daily in five doses in the active weeks and measuring effects on parameters of inflammation and pain. Although no anti-inflammatory effects of Δ-9-THC were detected during the trial, a highly significant reduction ($p < 0.001$) in additional analgesic requirements was achieved CS447.

**Fish poison.** Ethanol (95%) extract of the dried aerial parts at a concentration of 1:1 was active. The water extract was inactive CS443.

**Follicle-stimulating hormone release inhibition.** Ethanol (95%) extract of the dried resin, administered intraperitoneally to toads at a dose of 10 mg/day for 14 days, was active. The results were significant at $p < 0.01$ level CS216.

**Food intake modulation.** Cannabis sativa stimulates appetite, especially for sweet and palatable food. Cannabinoid action has proposed a central role of the cannabinoid system in obesity CS351. Dronabinol, a commercially available form of THC, has been used successfully for increasing appetite in patients with HIV wasting disease. Cannabinoid receptor antagonist may reduce obesity CS352. To determine the prevalence of substance use in adolescents with eating disorders, the results of a data set of Ontario high school students were compared. One hundred and one female adolescents who met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition’s criteria for an eating disorder were followed up in a tertiary care pediatric treatment center. They were asked to participate in a cross-sectional study using a self-administered questionnaire assessing substance use and investigating reasons for use and nonuse; 95 agreed to participate and 77 completed the questionnaire (mean age, 15.2 years). The patients were divided into two groups: 63 with restrictive symptoms only, 17 with purging symptoms. The rates of drug use between subjects and their comparison groups were compared by Z-scores, with the level of significance set at 0.05. During the preceding year, restrictors used significantly less tobacco, alcohol, and cannabis than grade- and sex-matched comparison populations, and purgers used these substances at rates similar to those of comparison subjects. Other drugs seen frequently in the purgers included hallucinogens, tranquilizers, stimulants, LSD, phencyclidine, cocaine, and ecstasy. Both groups used caffeine and laxatives, but few used diet pills. Restrictors said they did not use substances because they were bad for their health, tasted unpleasant, were contrary to their beliefs, and were too expensive. Purgers generally used substances to relax, relieve anger, avoid eating, and “get away” from problems. Female adolescents with eating disorders who have restrictive symptoms use substances less frequently than the general adolescent population but do not abstain from their use. Those with purging symptoms use substances with a similar frequency to that found in the general adolescent population CS372.

**Gastric secretory inhibition.** Petroleum ether extract of the dried aerial parts, administered intraperitoneally to male rats, was active CS097.

**Gene expression effect.** Cannabinoids can cross the placental barrier and be secreted in the maternal milk. Through this way, cannabinoids affect the ontogeny of various neurotransmitter systems leading to changes in different behavioral patterns. Dopamine and endogenous opioids are among the neurotransmitters that result more affected by perinatal cannabinoid exposure, which, when animals mature, produce changes in motor activity, drug-seeking behavior, nociception, and other processes. These disturbances are likely originated by the capa-
bility of cannabinoids to influence the expression of key genes for both neurotransmitters, in particular, the enzyme tyrosine hydroxylase and the opioid precursor proenkephalin. Cannabinoids seem to be able to influence the expression of genes encoding for neuroglia cell adhesion molecules, which supports a potential influence of cannabinoids on the processes of cell proliferation, neuronal migration or axonal elongation in which these proteins are involved. CB1 receptors, which represent the major targets for the action of cannabinoids, are abundantly expressed in certain brain regions, such as the subventricular areas, which have been involved in these processes during brain development. Cannabinoids might also be involved in the apoptotic death that occurs during brain development, possibly by influencing the expression of Bcl-2/Bax system. CB1 receptors are transiently expressed during brain development in different group of neurons which do not contain these receptors in the adult brain

**Glaucoma effect.** Nine patients with glaucoma unresponsive to treatment were treated with orally administered Δ9-THC capsules or inhaled cannabis in addition to their existing therapeutic regimen. An initial decrease in intraocular pressure was observed in all patients, and the investigator’s therapeutic goal was met in four of the nine patients. The decreases in intraocular pressure were not sustained, and the patients elected to discontinue treatment within 1–9 months for various reasons. Twenty-four percent of patients were reassured without intervention; 18% failed to attend follow-up.

**Hepatitis C risk factor.** The study of a dually diagnosed population estimated the prevalence of hepatitis C virus (HCV) to be...
29.7% or 16 times higher than that in the general population. A high correlation was found between the use of tobacco and HCV infection. This appears to be beyond the risk factor conveyed by intravenous drug use. Of the patients whose primary diagnoses were cocaine, opiate, amphetamine, or polysubstance dependence (drugs often used intravenously), 42% of the tobacco users were HCV-positive, whereas only 20% of the nontobacco using patients with similar primary diagnoses were HCV-positive. The association of tobacco use with HCV was found to be strong for females with alcohol, sedative/hypnotic, inhalant, or cannabis dependence, as none of the 17 nontobacco using female patients with these diagnoses were HCV-positive, whereas 14 of the 45 (31%) tobacco-using females with these diagnoses did test positive for HCV.

**Hepatotoxic activity.** Ethanol (95%) extract of the dried resin, administered intraperitoneally to toads at a dose of 10 mg/day for 14 days, was active. The results were significant at \( p < 0.01 \) level.[CS216]

**Histamine release stimulation.** Water extract of the seed, administered intradermally to human adults, was active on human basophils.[CS147]

**HIV involvement.** The prevalence, predictors, and patterns of cannabis use—specifically medicinal cannabis use among patients with HIV—were examined. Any cannabis use in the year prior to interview and self-defined medicinal use were evaluated. A cross-sectional multicenter survey and retrospective chart review were conducted to evaluate overall drug utilization in HIV, including cannabis use. HIV-positive adults were identified through the HIV Ontario Observational Database; 104 consenting patients were interviewed. Forty-three percent of the patients reported cannabis use, whereas 29% reported medicinal use. Reasons for use were similar by gender although a significantly higher number of women used cannabis for pain management. The most commonly reported reason for medicinal cannabis use was appetite stimulation/weight gain. Male gender and history of intravenous drug use were predictive of any cannabis use. Age, gender, HIV clinical status, antiretroviral use, and history of intravenous drug use were not significant predictors of medicinal cannabis use. Despite the frequency of medicinal use, minimal changes in the pattern of cannabis use on HIV diagnosis were reported with 80% of current medicinal users also indicating recreational consumption.[CS289] HIV patients (\( n = 252 \)) were recruited via consecutive sampling in public health care clinics. Structured interviews assessed patterns of recent cannabis use, including its perceived benefit for symptom relief. Associations between cannabis use and demographic and clinical variables were examined using univariate and multivariate regression analyses. Overall prevalence of smoked cannabis in the previous month was 23%. Reported benefits included relief of anxiety and/or depression (57%), improved appetite (53%), increased pleasure (33%), and relief of pain (28%). Recent use of cannabis was positively associated with severe nausea (OR = 4, \( p = 0.004 \)) and recent use of alcohol (OR = 7.5, \( p < 0.001 \)) and negatively associated with being Latino (OR = 0.07, \( p < 0.001 \)). No associations between cannabis use and pain symptoms were observed.[CS315] No safety problems specific to HIV or protease inhibitors were found in a study in which volunteers stayed in a research hospital 24 hours a day and were randomly assigned to either smoke cannabis, take oral THC, or take an oral placebo. Cannabis and THC use was associated with weight gain.[CS369]

**Hyperglycemic activity.** Ethanol (95%) extract of the leaf, administered intravenously to rats at a dose of 300 mg/kg, pro-
duced an increase of 40 mg percentage 2 hours postinjection and a corresponding decrease in liver glycogen\(^{67}\). Ethanol (95%) extract of the dried leaf, administered by gastric intubation to rabbits, produced an increase followed by a gradual decrease in blood sugar levels\(^{621}\). The dried leaves, smoked by human adults, produced elevated glucose levels in two out of four subjects and no impairment of insulin release or changes in growth hormone levels\(^{624}\).

**Hypertensive activity.** Ethanol (95%) and water extracts of the dried aerial parts, administered intravenously to cats, were inactive. The ethanol extract stimulated respiration and the water extract had no effect on respiration\(^{6243}\).

**Hypoglycemic activity.** Ethanol (95%) extract of the dried leaf, administered by gastric intubation to rabbits, produced an increase, followed by a gradual decrease, in blood sugar levels\(^{621}\). Extract of the dried leaf, administered subcutaneously to rabbits at a dose of 0.5 mL/kg (approx 0.6 mg THC) for 9 weeks, further enhanced hypoglycemia induced by insulin. No hypoglycemic effect was seen in normal animals\(^{6221}\). Hot water extract of the resin, administered by gastric intubation to dogs at a dose of 20 g of air-dried resin/animal, produced weak activity\(^{6198}\). The dried leaf, smoked by adults at a dose of 2 g/person, was inactive\(^{623}\).

**Hypotensive activity.** Ethanol (50%) extract of the entire plant, administered intravenously to dogs at a dose of 50 mg/kg, was active\(^{6207}\). Ethanol (95%) and water extracts of the dried aerial parts, administered intravenously to cats, were inactive. The ethanol extract stimulated respiration, and the water extract had no effect\(^{6243}\).

**Illicit drug in plasmapheresis donors.** Seventy-five US plasma units from 10 different states in the United States and 75 German plasma units that had been analyzed principally for their protein composition were screened for drugs. Determinations were made, using automated immunoassays, of the presence of cannabis, cocaine, amphetamine, methamphetamine, MDMA, methylenedioxymethylamphetamine (MDE), and opiates. Positive results were confirmed by gas chromatography–mass spectrometry. Eleven US plasma units were found to be positive for cocaine (14.6%), whereas all German samples were cocaine-negative (\(p = 0.0007\)). Fifteen US plasma units (20%) and one German unit (1.3%) were confirmed as positive for cannabis (\(p = 0.0003\)). Three out of 75 US plasma units were positive for both cannabis and cocaine. In none of the 150 samples were amphetamine, methamphetamine, MDMA, MDE, or opiates detected\(^{635}\).

**Immunomodulatory effect.** The smoking of cannabis showed a significant local immunosuppression of the bactericidal activity of human alveolar macrophages. In animal studies, cannabinoids were identified as potent modulators of cytokine production, causing a shift from T-helper-1 (Th1) to Th2 cytokines. In consequence, a compromised cellular immunity was observed in these animals, resulting in enhanced tumor growth and reduced immunity to viral infections. In vitro, immunosuppressive effects were shown in all immune cells, but only at high micromolar cannabinoid concentrations not reached under normal clinical conditions. In conclusion, there was no evidence that cannabinoids induce a serious, relevant immunosuppression in humans, with the exception of cannabis smoking, which may affect local bronchoalveolar immunity\(^{6279}\). The immune function in 16 MS patients treated with oral cannabinoids was measured. A modest increase of tumor necrosis factor (TNF)-\(\alpha\) in lipopolysaccharide-stimulated whole blood was found during cannabis plant-extract treatment (\(p = 0.037\)), with no change in other cytokines. In the subgroup of patients with high
adverse event scores, an increase in plasma IL-12p40 was found ($p = 0.002$). The results indicate pro-inflammatory disease-modifying potential of cannabinoids in MSC. THC and their metabolites inhibited production of IL-1 and $\gamma$-interferon, decreased a 33% of the lymphocytes activity and inhibited 66% of the lymphocytes adenylcyclase activity. The consumption of cannabis decreased immunological competence of macrophages, and alternated their essential role of trophicity of the central nervous system. Inhibiting actions of cannabinoids on the cyclo-oxygenase, promoted production of arachidonic acid degradation products. This compound mimics the action of histamine, induced a raise of the vascular permeability and bronchospasm, and contributed at delayed reaction of anaphylaxis.

**Infant mortality.** For a period of 11 months, 2964 infants were enrolled and screened at birth for exposure to cocaine, opiate, or cannabinoid by meconium analysis. At birth, 44% of the infants tested positive for drugs, 30.5% positive for cocaine, 20.2% for opiate, and 11.4% for cannabinoids. Compared with the drug-negative group, a significantly higher percentage ($p < 0.05$) of the drug-positive infants had lower weight and smaller head circumference and length at birth and a higher percent of their mothers were single, multigravid, multiparous, and had little to no prenatal care. Within the first 2 years of life, 44 infants died: 26 were drug-negative (15.7 deaths per 1000 live births) and 18 were drug-positive (13.7 deaths per 1000 live births). The mortality rate among cocaine, opiate, or cannabinoid-positive infants were 17.7, 18.4, and 8.9 per 1000 live births, respectively. Among infants with birth-weight of 2500 g or less, infants who were positive for both cocaine and morphine had a higher mortality rate (OR = 5.9, CI = 1.4–24) than drug-negative infants. Eleven infants died from the sudden infant death syndrome (SIDS); 58% were positive for drugs, predominantly cocaine. The odds ratio for SIDS among drug-positive infants was 1.5 (CI = 0.46–5.01) and 1.9 (CI = 0.58–6.2) among cocaine-positive infants.

**Infant neurobehavioral effect.** The subjects and controls in this study were full-term infants of appropriate gestational age with no medical problems. At 1–2 days of age, 20 infants exposed to cocaine, alcohol, cannabis, and cigarettes, 17 infants exposed to alcohol and/or cannabis and cigarettes, and 20 drug-free infants were evaluated by using the Neonatal Intensive Care Unit Network Neurobehavioral Scale. Cocaine-exposed (CE) infants showed increased tone and motor activity, more jerky movements, startles, tremors, back arching, and signs of central nervous system and visual stress than unexposed infants. They also showed poorer visual and auditory following. There were no differences in how the examination was administered to CE and nonexposed infants. Reduced birth-weight and length were also observed in CE infants. Differences attributable to CE infants were related to muscle tone and motor performance, following during orientation, and signs of stress. CE infants were not more difficult to test, nor did they require an alteration in the examination. Both neurobehavioral patterns of excitability and lethargy were observed. The findings may have been a result of the synergistic effects of cocaine with alcohol and cannabis.

**Inflammatory effect.** A case of a 17-year-old male regular cannabis user who developed a large swollen uvula (uvulitis) and partial upper airway obstruction after smoking cannabis was evaluated. Symptoms resolved with the administration of corticosteroids and antihistamines. A healthy 17-year-old man who inhaled cannabis prior to general anesthesia is described. In the recovery room, after an
uneventful general anesthetic, acute uvular edema resulted in postoperative airway obstruction and admission to the hospital. The uvular edema was treated successfully with dexamethasone.

**Information-processing effect.** Information processes are thought to represent the basic building blocks of higher order cognitive processes. The inspection time task was used to investigate the effects of acute and subacute cannabis use on information processing in 22 heavy users compared with 22 nonusers. The findings indicated that users in the subacute state display significantly slowed information-processing speeds (longer inspection times) compared with controls. This deficit appeared to be normalized while users were in the acute state. These results may be explained as a withdrawal effect, but may also be owing to tolerance development because of long-term cannabis use.

**Insecticidal activity.** Leaf extract, administered to larvae of *Chironomus samoensis*, produced paralysis leading to death. The extract brought a drastic change in the morphology of sensilla trichoidea, the general body cuticle, and a significant reduction in the concentration of magnesium and iron, whereas manganese showed only slight average increase. Because the sensilla trichoidea has nerve connections, it was assumed that the toxic principle of the leaf extract has affected the central nervous system.

**Intestinal motility activity.** Rat intestinal epithelial cells mounted in an Ussing chamber attached with voltage/current clamp were used for measuring changes of the short-circuit current across the epithelia. The intestinal epithelia were activated with current raised by serosal administration of forskolin $5 \mu \text{M}$. Ethanol extracts of cannabis augmented the current additively when each was added after forskolin. In subsequent experiments, ouabain, and bumetanide were added prior to ethanol extract of cannabis to determine their effect on Na$^+$ and Cl$^-$ movement. The results suggested that the extract may affect the Cl$^-$ movement more directly than Na$^+$ movement in the intestinal epithelial cell.

**Intraocular pressure reduction.** Polysaccharide fraction of the dried entire plant, administered intravenously to rabbits at a dose of $1 \mu \text{g/animal}$ was active. Water extract of the dried aerial parts, administered intravenously to rabbits at a dose of $250 \mu \text{g/animal}$, was active. A dose of $5 \mu \text{g/animal}$ was inactive on Rhesus monkeys and active on rabbits. A dose of $10 \text{mg/animal}$, administered per rectum to Rhesus monkeys and rabbits, was inactive.

**IQ effect.** Cannabis use for 70 individuals aged 17–20 years was determined through self-reporting and urinalysis. IQ scores were calculated by subtracting each person’s IQ score at 9–12 years (before initiation of drug use) from his or her score at 17–20 years. The difference in IQ scores of current heavy users (at least five joints per week), current light users (less than five joints per week), former users (who had not smoked regularly for at least 3 months), and nonusers (who never smoked more than once per week and no smoking in the past 2 weeks) was compared. Current cannabis use was significantly correlated ($p < 0.05$) in a dose-related fashion with a decline in IQ over the ages studied. The comparison of the IQ difference scores showed an average decrease of 4.1 points in current heavy users ($p < 0.05$) compared with gains in IQ points for light current users (5.8), former users (3.5), and nonusers (2.6).

**Lactate inhibition.** The dried leaf, smoked by adults at a dose of $2 \text{g/person}$, decreased blood lactic acid.

**Leutinizing hormone-release inhibition.** The dried aerial part, smoked by menopausal women at a dose of $1 \text{g/person}$, was inactive.

When administered to normal
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and castrated male rats, at a dose of 75 mg/kg, was active\textsuperscript{CS215}.

**Lower limb occlusive arteriopathy.** Seventy-three patients (60 males and 13 females less than 50 years of age) were divided into four groups: Buerger's disease (thromboangiitis obliterans [TAO]), atheromatous juvenile peripheral obstructive arterial diseases (POAD), autoimmune POAD, and arteriopathy of undetermined origin. The first symptoms occurred at 38 ± 8 years of age. Fourteen patients (20%) had TAO, 51 (70%) atheromatous POAD, 4 (5%) POAD with systemic or autoimmune disease, and 4 (5%) undetermined POAD. Age of onset was earlier in TAO (35 ± 8 vs 40 ± 8 years, \( p = 0.046 \)), smoking was greater in the atheroma group (33 ± 16 vs 24 ± 14 pack/years, \( p = 0.033 \)). Fifty-three patients with POAD had dyslipidemia and 26% had hypertension. Regular cannabis intake was more frequent in the TAO group (21% vs 8%). At the time of medical care, Fontaine's stage was more frequently stage II in atheroma patients (57% vs 14%) and stage IV in TAO patients (86% vs 35%). TAO was diagnosed in 43% cannabis users and in 19% nonusers. Results indicated that the main etiology of juvenile POAD is atheroma, followed by TAO. Cannabis users accounted for at least 10% of these patients. They were characterized by lower tobacco intake, more distal lesions, more frequent involvement of the upper limbs. They presented more frequently as TAO\textsuperscript{CS197}. A case of a 30-year-old woman who smoked cannabis and developed intermittent claudication of the lower limbs was reported. Results indicated that cannabis could be involved not only in the pathogenesis of juvenile obstructive arteriopathy, but also in the development of atheromatous lesions\textsuperscript{CS409}.

**Lung function.** A group of over 900 young adults derived from a birth cohort of 1037 subjects were studied at age 18, 21, and 26 years. Cannabis and tobacco smoking were documented at each age using a standardized interview. Lung function, as measured by the FEV\textsubscript{1}–vital capacity (VC) ratio, was obtained by simple spirometry. A fixed effects regression model was used to analyze the data and to account for confounding factors. When the sample was stratified for cumulative use, there was evidence of a linear relationship between cannabis use and FEV\textsubscript{1}–VC (\( p < 0.05 \)). In the absence of adjusting for other variables, increasing cannabis use over time was associated with a decline in FEV\textsubscript{1}–VC with time; the mean FEV\textsubscript{1}–VC among subjects using cannabis on 900 or more occasions was 7.2, 2.6 and 5% less than nonusers at ages 18, 21, and 26, respectively. After controlling for potential confounding factors (age, tobacco smoking, and weight) the negative effect of cumulative cannabis use on mean FEV\textsubscript{1}–VC was only marginally significant (\( p < 0.09 \)). Age (\( p < 0.001 \)), cigarette smoking (\( p < 0.05 \)), and weight (\( p < 0.001 \)) were all significant predictors of FEV\textsubscript{1}–VC. Cannabis use and daily cigarette smoking acted additively to influence FEV\textsubscript{1}–VC. Results indicated that longitudinal observations over 8 years in young adults revealed a dose-dependent relationship between cumulative cannabis consumption and decline in FEV\textsubscript{1}–VC. When confounders were accounted for the effect was reduced and was only marginally significant, but given the limited time frame over which observations were made, the trend suggests that continued cannabis smoking has the potential to result in clinically important impairment of lung function\textsuperscript{CS371}.

**Luteolytic effect.** The aerial parts, smoked by a chronic high-dose user, were inactive\textsuperscript{CS160}.

**Memory impairment.** The effects of combined exposure to ethanol and Δ-9-THC in a memory task was investigated in rats. Ethanol, voluntarily ingested in alcohol-
preferring rats, and THC, given by intraperitoneal injection, had a synergic action to impair object recognition when a 15-minute interval was adopted between the sample phase and the choice phase of the test. Ingestion of ethanol, or 2 or 5 mg/kg of THC were not able to modify object recognition in these experimental conditions. When voluntary ethanol ingestion was combined with administration of these doses of THC, object recognition was markedly impaired. THC impaired object recognition only at the dose of 10 mg/kg, when its administration was not combined with that of ethanol. The selective cannabinoid CB1 receptor antagonist SR 141716A (N-(piperidin-1-yl)-5-(4-chlorophenyl)-1(2, 4-dichloro-phenyl)-4-methyl-1H-pyrazole carboxamide HCl) at the dose of 1 mg/kg reversed the amnesic effect of 10 mg/kg of THC. This indicated that the effect is mediated by the receptor subtype. The synergism of ethanol and THC was not detected when an intertrial interval of 1 minute was adopted\textsuperscript{CS370}.

**Memory improvement.** Extract from fructus cannabis (EFC), administered intragastrically to mice with drug-induced dysnesia at doses of 0.2, 0.4, and 0.8 g/kg, for 7 days, prolonged the latency and decreased the number of errors in the step-down test, and enhanced the spatial resolution of amnesic mice in water maze test. EFC at the dose of 0.2 g/kg overcame amnesia of three stages of memory process. EFC activated calcineurin activity at a concentration range of 0.01–100 g/L. The maximal value of EFC on calcineurin activity (35% \(\pm 5\%\)) appeared at a concentration of 10 g/L\textsuperscript{CS310}. EFC with activation of calcineurin, extracted from Chinese traditional medicine, was used to determine the effects on memory and immunity in mice. In the step-down-type passive avoidance test, the plant extract (0.2 g/kg) significantly improved amnesia induced by drugs, and greatly enhanced the ability of cell-mediated type hypersensitivity and nonspecific immune responses in normal mice\textsuperscript{CS134}.

**Mitochondrial function disruption.** \(\Delta 9\)-THC in the pulmonary transformed cell line A549 produced a rapid and extensive depletion of cellular energy stores. Adenosine 5'-triphosphatase levels declined dose dependently with an IC\textsubscript{50} of 7.5 \(\mu\)g/mL of THC after 24 hours of exposure. Cell death was observed only at concentrations greater than 10 \(\mu\)g/mL. Studies using JC-1, a fluorescent probe for mitochondrial membrane potential, revealed diminished mitochondrial function at THC concentrations as low as 0.5 \(\mu\)g/mL. At concentrations of 2.5 and 10 \(\mu\)g/mL of THC, a decrease in mitochondrial membrane potential was observed 1 hour after THC exposure. Mitochondrial function remained diminished for at least 30 hours after THC exposure. Flow cytometry studies on cells exposed to particulate smoke extracts indicated that JC-1 red fluorescence was fivefold lower in cells exposed to cannabis smoke extract compared with tobacco smoke-exposed cells. Comparison with a variety of mitochondrial inhibitors demonstrated that THC produced effects similar to that of carbonyl cyanide \(p\)-trifluoromethoxyphenylhydrazone, suggesting uncoupling of electron transport. Loss of red JC-1 fluorescence by THC was suppressed by cyclosporin A, suggesting mediation by the mitochondrial permeability transition pore. This disruption of mitochondrial function was sustained for at least 24 hours after removal of THC by extensive washing\textsuperscript{CS360}.

**Mitogenic effect.** The resin was inactive on the human and rat white blood cells\textsuperscript{CS037}.

**Molluscicidal activity.** Ethanol (95%) and water extracts of the dried flowering tops, at a concentration of 1000 ppm, produced weak activity on Biomphalaria straminea and Biomphalaria glabrata\textsuperscript{CS245}. Water saturated with essential oil of the aerial parts, at a con-
centration of 1:2, produced weak activity on Biomphalaria glabrata. **Motor function.** Nine cannabis smokers and 16 controls were studied to determine the attentional areas related to motor function, and primary and supplementary motor cortices. Echo planar images and high-resolution molecular resonance images were acquired. The challenge paradigm included left and right finger sequencing. Group differences in cerebral activation were examined for Brodmann areas (BA) 4, 6, 24, and 32 using region of interests analyses in statistical parametric mapping. Cannabis users, tested within 4–36 hours of discontinuation, exhibited significantly less activation than controls in BA 24 and 32 bilaterally during right- and left-sided sequencing and for BA 6 in all tasks except for left-sided sequencing in the left hemisphere. There were no statistically significant differences for BA 4. None of these regional activations correlated with urinary cannabis concentration and verbal IQ for smokers. The results suggested that recently abstinent chronic cannabis smokers produce reduced activation in motor cortical areas in response to finger sequencing compared with controls.

**Multiple sclerosis.** One hundred fifty-seven drug-naïve, first-episode schizophrenic patients were examined. A significantly elevated brain-derived neurotrophic factor (BDNF) serum concentrations in patients with chronic cannabis abuse (n = 35, p < 0.001) or multiple substance abuse (n = 20, p < 0.001) prior to disease onset were found. Drug-naïve schizophrenic patients without cannabis consumption showed similar results to normal controls and cannabis controls without schizophrenia. Elevated BDNF serum levels were not related to schizophrenia and/or substance abuse itself but may reflect a cannabis-related idiosyncratic damage of the schizophrenic brain. Disease onset was 5.2 years earlier in the cannabis-consuming group (p = 0.0111). A cannabis-based medicinal extract (CBME) was administered to 160 patients with multiple sclerosis experiencing significant problems from at least one of the following: spasticity, spasms, bladder problems, tremor, or pain. The interventions were oromucosal sprays of matched placebo, or whole plant CBME containing equal amounts of Δ-9-THC and CBD at a dose of 2.5–120 mg of each daily, in divided doses. The primary outcome measure was a Visual Analogue Scale (VAS) score for each patient’s most troublesome symptom. Additional measures included VAS scores of other symptoms, and measures of disability, cognition, mood, sleep and fatigue. Following CBME the primary symptom score reduced from mean 74.36 (11.1) to 48.89 (22.0) following CBME and from 74.31 (12.5) to 54.79 (26.3) following placebo. Spasticity VAS scores were significantly reduced by CBME (Sativex®) in comparison with placebo (p = 0.001). There were no significant adverse effects on cognition or mood and intoxication was generally mild. A SCE with pure Δ-9-THC, at matched concentrations of Δ-9-THC, and a Δ-9-THC-free extract (Δ-9-THC-free SCE) in a mouse model of MS, were examined. Although SCE inhibited spasticity in the mouse model of MS to a comparable level, it caused a more rapid onset of muscle relaxation and a reduction in the time to maximum effect compared with Δ-9-THC alone. The Δ-9-THC-free extract or CBD caused no inhibition of spasticity. In an experimental allergic encephalomyelitis (EAE), an animal model of MS, it was demonstrated that the cannabinoid system is neuroprotective during EAE. Mice, deficient in the cannabinoid receptor CB1, tolerated inflammatory and excitotoxic insults poorly, and developed substantial neurodegeneration following immune attack in EAE. Exogenous CB1 agonists can provide significant neuroprotection from...
the consequences of inflammatory central nervous system disease in an experimental allergic uveitis model\textsuperscript{(CS339)}.

**Mutagenic activity.** Petroleum ether extract of the aerial parts, in the ration of *Drosophila* at concentrations of 0.5, 1, and 5% of the diet, was active\textsuperscript{(CS190)}. Petroleum ether extract of the dried leaf, administered by gastric intubation to male mice at a dose of 50 mg/kg, was active\textsuperscript{(CS183)}. Water and methanol extracts of the seed, on agar plate at a concentration of 100 mg/mL, were inactive on *Bacillus subtilis* H-17 (Rec+) and *Salmonella typhimurium* TA100 and TA98. Metabolic activation had no effect on the results\textsuperscript{(CS199)}.

**Myocardial infarction.** A young man who suffered a myocardial infarction after taking Viagra\textsuperscript{(8)} in combination with cannabis was investigated. Viagra is metabolized predominantly by the CYP450 3A4 hepatic microsomal isoenzyme. Cannabis is a known inhibitor of CYP450 3A4 isoenzyme. The effect of the Viagra was thus potentiated by the effect of cannabis\textsuperscript{(CS387)}.

**Natural-killer cells effect.** Leukemia susceptible BALB/c and resistant C57BL/6 mice were infected with Friend leukemia virus complex and its helper component Rowson-Parr virus. At different time points, their natural-killer cells were separated from spleens and treated with 0–10 \(\mu g/mL\) of THC, subsequently mixed with Yac-1 target cells for 4 and 18 hours. The natural-killer cell activity in both mouse strains infected by either virus complex or helper virus weakened on days 2–4 postinfection, normalized by day 8 and enhanced on days 11–14. Natural-killer cell activity on the effect of low concentration (1–2.5 \(\mu g/mL\)) of THC slightly increased in BALB/c, was unaffected in C57BL/6, especially in the 18 hour assays. In the combined effects of cannabis and retrovirus, damages by cannabis dominated over those of retroviruses. Inhibition or reactive enhancement of natural-killer cell activity on the effect of viruses were similar to those of infected but cannabis-free counterparts, but on the level of uninfected cells treated with cannabis. The effects of cannabis and retrovirus were additive resulting in anergy of natural-killer cells\textsuperscript{(CS412)}.

**Neonatal abstinence syndrome.** The relationship of maternal drug abuse to symptoms, the effectiveness of pharmacological agents in controlling symptoms, and the length of in-patient stay were investigated in infants with neonatal abstinence syndrome. Pharmacological treatment was oral morphine sulphate (0.2 mg four to six times hourly), phenobarbitone (3–7 mg/kg/day), or combination of the two were administered to infants with a serial Finnegan score greater than 8. The average maternal age was 24.6 years, (18–34 years). Drug use volunteered by the mothers was methadone alone in 6 cases, methadone and benzodiazepines in 14, methadone and heroin and benzodiazepines in 7, methadone and heroin in 10, heroin alone in 2, and other multiple drug use including oral morphine sulphate, dothiepin, and cannabis in 4.

Average gestational age was 40.3 (35–42 weeks). The average birth-weight was 2.81 kg (1.89–3.91 kg). Time-to-onset of withdrawal symptoms was 2.8 (1–13) days. The duration of pharmacological treatment (oral morphine sulphate and/or phenobarbitone) was 21.8 (1–62) days. The total hospital stay for the 43 infants was 1011 days\textsuperscript{(CS424)}.

**Neuroendocrine abnormalities.** Prolactin response to D-fenfluramine was assessed in abstinent ecstasy (MDMA) users with concomitant use of cannabis only (13 males, 11 females) and in two control groups: healthy nonusers (13 females) and exclusive cannabis users (seven males). Prolactin response to D-fenfluramine was slightly blunted in female ecstasy users. Both male user samples exhibited a weak prolactin response to D-fenfluramine, but this was
weaker in the group of cannabis users. Baseline prolactin and prolactin response to D-fenfluramine were associated with the extent of previous cannabis use. The results indicated that the endocrinological abnormalities of ecstasy users might be closely related to their coincident cannabis use.

**Neurogenic symptoms alleviation.** Whole-plant extracts of Δ-9-THC, CBD, 1:1 CBD:THC, or placebo were self-administered by sublingual spray to 24 patients with MS (n = 18), spinal cord injury (n = 4), brachial plexus damage (n = 1), and limb amputation owing to neurofibromatosis (n = 1), at doses determined by titration against symptom relief or unwanted effects within the range of 2.5–120 mg/24 hours for 2 weeks. The patients recorded symptoms, wellbeing, and intoxication scores on a daily basis using visual analog scales. At the end of each two-week period an observer rated severity and frequency of symptoms on numerical rating scales, administered standard measures of disability (Barthel Index), mood, cognition, and recorded adverse events. Pain relief associated with both THC and CBD was significantly superior to placebo. Impaired bladder control, muscle spasms, and spasticity were improved by cannabis medicinal extract (CME) in some patients with these symptoms. Three patients had transient hypotension and intoxication with rapid initial dosing of THC-containing CME. The results indicated that cannabis could improve neurogenic symptoms unresponsive to standard treatments. Unwanted effects were predictable and generally well tolerated.

**Neuropathic pain relief.** Forty-eight patients with at least one avulsed root and baseline pain score of four or more on an 11-point ordinate scale participated in a randomized, double-blind, placebo-controlled, three-period crossover study. The patients had intractable symptoms regardless of current analgesic therapy. They entered a baseline period of 2 weeks, followed by three, 2-week treatment periods; during each period they received one of three oromucosal spray preparations. These were placebo and two whole plant extracts of C. sativa L.: GW-1000-02 (Sativex®), containing Δ-9-THC: CBD in an approx 1:1 ratio and GW-2000-02, containing primarily THC. The primary outcome measure was the mean pain severity score during the last 7 days of treatment. Secondary outcome measures included pain related quality of life assessments. The primary outcome measure failed to fall by the two points defined in our hypothesis. Both this measure and measures of sleep showed statistically significant improvements. The study medications were well tolerated with the majority of adverse events, including intoxication type mild to moderate in severity and resolving spontaneous reactions.

**Neuroprotective effect.** The effect of cannabidiol on β-amyloid peptide-induced toxicity in cultured rat pheocromocytoma PC12 cells was investigated. Following exposure of cells to β-amyloid peptide (1 µg/mL), a marked reduction in cell survival was observed. This effect was associated with increased reactive oxygen species production and lipid peroxidation, and caspase 3 (a key enzyme in the apoptosis cell-signalling cascade) appearance, DNA fragmentation, and increased intracellular calcium. Treatment of the cells with CBD (10−7−10−4 mol) prior to β-amyloid peptide exposure, significantly elevated cell survival, whereas it decreased reactive oxygen species production, lipid peroxidation, caspase 3 levels, DNA fragmentation, and increased intracellular calcium. CBD and other cannabinoids were examined as neuroprotectants in rat cortical neuron cultures exposed to toxic levels of glutamate. The psychotropic cannabinoid receptor agonist Δ-9-THC and cannabidiol, reduced N-methyl-D-aspartate,
α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid and kainate receptor mediated neurotoxicities. Neuroprotection was not affected by cannabinoid receptor antagonist, indicating a (cannabinoid) receptor-independent mechanism of action. CBD demonstrated a reduction in hydroperoxide toxicity in neurons. In this trial of the abilities of various antioxidants to prevent glutamate toxicity, cannabidiol was superior to both α-tocopherol and ascorbate in protective capacity CS412.

Neuropsychological effect. Cerebral blood flow was measured in 12 long-term cannabis users shortly after cessation of cannabis use (mean 1.6 days). The findings showed significantly lower mean hemispheric blood flow values and significantly lower frontal values in the cannabis subjects compared with normal controls. The results indicated that the functional level of the frontal lobes was affected by long-term cannabis use CS397.

Neurotransmission inhibition. The BLA or the medial prefrontal cortex (PFC) stimulation in urethane-anesthetized rats induced generation of action potentials in the Nac neurons. This excitatory effect was strongly inhibited by the synthetic cannabinoid agonists WIN (0.062–0.25 mg/kg, iv [intravenously]) and HU-210 (0.125–0.25 mg/kg, iv), or Δ9-THC (1 mg/kg, iv). D1 or D2 dopamine receptor antagonists (SCH23390 0.5–1 mg/kg, sulpiride 5–10 mg/kg, iv) or the opioid antagonist naloxone (1 mg/kg, iv) were not able to reverse the action of cannabinoids. The selective CB1 receptor antagonist/reverse agonist SR141716A (0.5 mg/kg, iv) fully suppressed the action of cannabinoid agonists, whereas per se had no significant effect CS374.

Nicotine and Δ9-THC interaction. Δ9-THC administration to mice significantly decreased the incidence of several nicotine withdrawal signs precipitated by mecamylamine or naloxone, such as wet-dog-shakes, paw tremor, and scratches. In both experimental conditions, the global withdrawal score was significantly attenuated by Δ9-THC administration. The effect of Δ9-THC was not to the result possible adaptive changes induced by chronic nicotine on CB1 cannabinoid receptors. The density and functional activity of these receptors were not modified by chronic nicotine administration in the different brain structures investigated. The consequences of Δ9-THC administration on c-Fos expression in several brain structures after chronic nicotine administration and withdrawal were examined. c-Fos was decreased in the caudate putamen and the dentate gyrus after mecamylamine precipitated nicotine withdrawal. Δ9-THC administration did not modify c-Fos expression under these experimental conditions. Δ9-THC also reversed conditioned place aversion associated to naloxone precipitated nicotine withdrawal. The results indicated that Δ9-THC administration attenuated somatic signs of nicotine withdrawal and this effect was not associated with compensatory changes on CB1 cannabinoid receptors during chronic nicotine administration. Δ9-THC also ameliorated the aversive motivational consequences of nicotine withdrawal CS253.

Night vision improvement. In a double-blind study, graduated THC administration at doses of 0–20 mg (as Marinol) on measures of dark adaptometry and scotopic sensitivity was evaluated. Field studies of night vision were performed among Jamaican and Moroccan fishermen, and mountain dwellers with the LKC Technologies Scotopic Sensitivity Tester-1 (SST-1). Improvements in night vision measures were noted after THC or cannabis. The effect was dose-dependent and cannabinoid-mediated at the retinal level CS286.

Nocturnal sleep effect. Eight healthy volunteers (four males, four females; aged 21–
34 years) were taking placebo, 15 mg Δ-9-THC, 5 mg THC combined with 5 mg CBD, and 15 mg THC combined with 15 mg CBD. These were formulated in 50:50 ethanol to propylene glycol and administered using an oromucosal spray during a 30-minute period from 10 PM. Electroencephalogram was recorded during the sleep period (11 PM to 7 AM). Performance, sleep latency, and subjective assessments of sleepiness and mood were measured from 8:30 AM (10 hours after drug administration). There were no effects of 15 mg THC on nocturnal sleep. With the concomitant administration of the drugs (5 mg THC and 5 mg CBD to 15 mg THC and 15 mg CBD), there was a decrease in stage 3 sleep, and with the higher dose combination, wakefulness was increased. The next day, with a 15-mg THC dose, memory was impaired, sleep latency was reduced, and the subjects reported increased sleepiness and changes in mood. With the lower dose combination, reaction time was faster on the digit recall task, and with the higher dose combination, subjects reported increased sleepiness and changes in mood. Fifteen milligrams of THC appeared to be sedative, and 15 mg CBD appeared to have alerting properties as it increased waking activity during sleep and counteracted the residual sedative activity of the 15 mg THC.

**Occipital stroke.** A right occipital ischemic stroke occurred in a 37-year-old Albanese man with a previously uneventful medical history, 15 minutes after smoking a cigarette with approximately 250 mg of cannabis. Clinical manifestations of the stroke were left-sided hemiparesis, hemihypesthesia and blurred vision, which vanished spontaneously and almost completely after 3 days. The patient has been smoking cannabis regularly from the age of 27, with a frequency of two to three cigarettes/cannabis per week during the 6 months that preceded his stroke. Except for cigarette smoking and slight dyslipidemia, classical risk factors for stroke/embolism were absent. The family history for cerebrovascular events, blood pressure, clotting tests, examinations for thrombophilia, vasculitis, extracranial and intracranial arteries, and cardiac investigations were normal or respectively negative; the stroke was attributed to the chronic cannabis consumption.

**Oral cancer.** A study of 116 patients aged 45 years and younger, diagnosed with squamous cell carcinoma of the mouth was conducted. Two hundred and seven controls who had never had cancer, matched for age, sex, and area of residence, were recruited. The self-completed questionnaire contained items about exposure to the following risk factors: tobacco products, cannabis, alcohol, and diet. Conditional logistic analyses were conducted adjusting for social class, ethnicity, tobacco, and alcohol habits. All tests for statistical significance were two-sided. The majority of oral cancer patients reported exposure to the major risk factors of tobacco and alcohol even at the younger age. The estimated risks associated with tobacco or alcohol were low (OR range: 0.6–2.5) among both males and females. Only smoking for 21 years or more produced significantly elevated odds ratios (OR = 2.1; 95% CI: 1.1–4). Exposure associated with other major risk factors did not produce significant risks in this sample. Long-term consumption of fresh fruits and vegetables in the diet appeared to be protective for both males and females.

**Oral cytological effect.** The effects of cannabis, methaqualone, or tobacco smoking on the epithelial cells in 16 patients were evaluated. The site samples included the buccal mucosa (left and right sides), the posterior dorsum of the tongue, and the anterior floor of the mouth. There was a
significant prevalence of bacterial cells in the smears and a greater number of degenerate and atypical squamous cells in cannabis users compared with controls. Epithelial cells in smears taken from cannabis users and tobacco-smoking controls showed koilocytic changes\textsuperscript{CS176}.

**Ovulation inhibition effect.** Petroleum ether extract of the aerial parts, administered orally to rats, produced weak activity\textsuperscript{CS087}.

**Pancreatic effect.** A 29-year-old man presented with acute pancreatitis after a period of heavy cannabis smoking. Other causes of the disease were ruled out. The pancreatitis resolved itself after the cannabis was stopped and this was confirmed by urinary cannabinoid metabolite monitoring in the community. There were no previous reports of acute pancreatitis associated with cannabis use in the general population. Drugs of all types are related to the etiology of pancreatitis in approximately 1.4–2\% of cases\textsuperscript{CS131}.

**Pancreatic toxicity.** The dried leaf, smoked by a 19-year-old woman, was active. The subject was hospitalized with pancreatitis\textsuperscript{CS220}.

**Panic disorder.** Sixty-six panic disorder patients were included in a study. All of whom met the DSM-IV diagnosis of panic disorder (\(n = 45\)) or panic disorder with agoraphobia ([PDA]; \(n = 21\)). Twenty-four patients experienced their first panic attack within 48 hours of cannabis use and then went on to develop panic disorder. All the patients were treated with paroxetine (gradually increased up to 40 mg/day). The two groups responded equally well to paroxetine treatment as measured at the 8 weeks and 12 months follow-up visits. There were no significant effects of age, sex, and duration of illness as covariates with response rates between the two groups. In addition, panic disorder or panic disorder with agoraphobia diagnosis did not affect the treatment response in either group. There were no significant differences in weight gain, sexual side effects, or relapse rates between patients according to gender or comorbid diagnosis\textsuperscript{CS300}.

**Paroxysmal atrial fibrillation.** A healthy young subject was observed for paroxysmal atrial fibrillation following cannabis intoxication. The abuse of this substance was the most possible and identifiable risk factor\textsuperscript{CS407}.

**Place conditioning effect.** THC was administered to female rats at doses of 1, 5, or 20 mg/kg) during gestation and lactation. Maternal exposure to low doses of THC (1 and 5 mg/kg), relevant for human consumption, produced an increased response to the reinforcing effects of a moderate dose of morphine (350 \(\mu\)g/kg), as measured in the place-preference conditioning paradigm (CPP) in the adult male offspring. These animals also displayed an enhanced exploratory behavior in the defensive withdrawal test. Only females born from mothers exposed to THC at a dose of 1 mg/kg exhibited a small increment in the place conditioning induced by morphine. The possible implication of the HPA was analyzed by monitoring plasma levels of adrenocorticotropic hormone (ACTH) and corticosterone in basal and moderate-stress conditions (after the end of the CPP test). Female offspring perinatally exposed to THC (1 or 5 mg/kg) displayed high basal levels of corticosterone and a blunted adrenal response to the HPA-activating effects of the CPP test. Male offspring born from mothers exposed to THC (1 or 5 mg/kg) displayed the opposite pattern: normal to low basal levels of corticosterone, and a sharp adrenal response to the CPP challenge\textsuperscript{CS436}.

THC administration to rats at a low dose (1.5 mg/kg) resulted in failing to develop place conditioning, and developing a place aversion at a high dose (15 mg/kg). Admin-
istration of the cannabinoid antagonist SR141716A induced a CPP at both a low (0.5 mg/kg) and a high (5 mg/kg) dose.\textsuperscript{CS41}

**Plant germination effect.** Methyl chloride extract of the dried seed produced weak activity on *Amaranthus spinosus* (25.8%) inhibition.\textsuperscript{CS176} Methyl chloride extract of the dried leaves produced 17.5% inhibition of *Amaranthus spinosus*.\textsuperscript{CS176}

**Plasma norepinephrine concentration.** Forty-six newborn infants participated in a prospective study of the neonatal and long-term effects of prenatal cocaine exposure. Based on maternal self-report, maternal urine screening, and infant meconium analysis, 24 infants were classified as CE and 22 as unexposed. Between 24 and 72 hours postpartum, plasma samples for norepinephrine (NE), epinephrine, dopamine, and dihydroxyphenylalanine analysis were obtained. The Neonatal Behavioral Assessment Scale was administered at 1–3 days of age and at 2 weeks of age by examiners masked to the drug exposure status of the newborns. The CE newborns had increased plasma NE concentrations when compared with the unexposed infants (geometric mean, 923 pg/mL vs 667 pg/mL). There were no significant differences in plasma epinephrine, dopamine, or dihydroxyphenylalanine concentrations. Analysis for the effect of potential confounding variables revealed that maternal cannabis use was also associated with increased plasma NE, although birth-weight, gender, and maternal use of alcohol or cigarettes were not. Geometric mean plasma NE was 1164 pg/mL in those infants with in utero exposure to both cocaine and cannabis compared to 812 pg/mL in those exposed to only cocaine and 667.0 pg/mL in those exposed to neither. Among the CE infants, plasma NE concentration correlated with an increased score for the depressed cluster ($r = 0.53$) and a decreased score for the orientation cluster ($r = -0.43$) of the Neonatal Behavioral Assessment Scale administered at 1–3 days of age. Adjusting for cannabis exposure had no effect on these relationships between plasma NE and the depressed and orientation clusters.\textsuperscript{CS49}

**Pneumonic effect.** A case–control study was conducted in 7001 individuals. Odds ratios were calculated by conditional logistic regression with substance use and social factors as cofounders. Pneumonia was not associated with kava use. Crude odds ratios $= 1.26$ (0.74–2.14, $p = 0.386$) increased after controlling for confounders (OR = 1.98, 0.63–6.23, $p = 0.237$) but was not significant. Adjusted odds ratios for pneumonia cases involving kava and alcohol users was 1.19 (0.39–3.62, $p = 0.756$). Crude odds ratios for associations between pneumonia and cannabis use (OR = 2.27, 1.18–4.37, $p = 0.014$) and alcohol use (OR = 1.95, 1.07–3.53, $p = 0.026$) were statistically significant and approached significance for petrol sniffing (OR = 1.98, 0.99–3.95, $p = 0.056$).\textsuperscript{CS335}

**Postural syncope.** Twenty-nine volunteers participated in a randomized, double-blind, placebo-controlled study. Cerebral blood velocity, pulse rate, blood pressure, skin perfusion on forehead and plasma ∆9-THC levels were quantified during reclining and standing for 10 minutes before and after THC infusions and cannabis smoking. Both THC and cannabis induced postural dizziness, with 28% reporting severe symptoms. Intoxication and dizziness peaked immediately after drug. The severe dizziness group showed the most marked postural drop in cerebral blood velocity and blood pressure and showed a drop in pulse rate after an initial increase during standing. Postural dizziness was unrelated to plasma levels of THC and other indices.\textsuperscript{CS340}

**Prenatal exposure.** Data collected from the National Household Survey on Drug Abuse, a nationally representative sample survey of 22,303 noninstitutionalized women aged
18–44 years, of whom 1249 were pregnant, were analyzed. During the 2-year study period, 6.4% of the non-pregnant women of childbearing age and 2.8% of the pregnant women reported that they used illicit drugs. Of the women who used drugs, the relative proportion of women who abstained from illicit drugs after recognition of pregnancy increased from 28% during the first trimester of pregnancy to 93% by the third trimester. However, because of postpregnancy relapse, the net pregnancy-related reduction in illicit drug use at postpartum was only 24%. Cannabis accounted for three-fourths of illicit drug use, and cocaine accounted for one-tenth of illicit drug use. Of those who used illicit drugs, over half of pregnant and two-thirds of non-pregnant women used cigarettes and alcohol. Among the sociodemographic subgroups, pregnant and non-pregnant women who were young (18–30 years) or unmarried, and pregnant women with less than a high school education had the highest rates of illicit drug use. Over 12,000 women at 18–20 weeks of gestation were enrolled in an Avon Longitudinal Study of Pregnancy and Childhood. Five percent of the mothers reported smoking cannabis before and/or during pregnancy; they were younger, of lower parity, better educated, and more likely to use alcohol, cigarettes, coffee, tea, and hard drugs. Cannabis use during pregnancy was unrelated to risk of perinatal death or need for special care, but the babies of women who used cannabis at least once per week before and throughout pregnancy were 90 g lighter than the offspring of other women. No significant adjusted effects were seen for birth length and head circumference. In two hospitals, 12,885 pregnant women answered questionnaires regarding consumption of alcohol, tobacco, cannabis, and other drugs. The prevalence of cannabis use was 0.8%. Women using cannabis, but no other illicit drugs were each retrospectively matched with four randomly chosen pregnant women in the same period and the same age group and with same parity. Eighty-four cannabis users were included. These women were socioeconomically disadvantaged and had a higher prevalence of present and past use of alcohol, tobacco, and other drugs. No significant difference in pregnancy, delivery, or puerperal outcome was found. Children of women using cannabis were 150 g lighter, 1.2 cm shorter, and had 0.2 cm smaller head circumference than the control infants. A 27-year-old woman who smoked a joint (cannabis) and 20 cigarettes (tobacco) daily up to the time of a positive pregnancy test at 7 weeks and 4 days, was evaluated. On day 20 of pregnancy, she had a LSD minitrip. The patient had a spontaneous term delivery. The baby boy weight was between the 5th and the 50th percentile, length between the 50th and the 90th percentile, normal umbilical arterial and venous pH values, and Apgar scores of 7/9/10. There were no visible abnormalities, and behavior was normal. Eight hundred seven consecutive positive-pregnancy test urine samples were screened for a range of drugs, including cotinine as an indicator of maternal smoking habits. A positive test for cannabinoids was found in 117 (14.5%) of the samples. Smaller numbers of samples were positive for other drugs: opiates (11), benzodiazepines (4), cocaine (3), and one each for amphetamines and methadone. Polydrug use was detected in nine individu-
als. Only two samples tested positive for ethanol. The proportion with a urine cotinine level indicative of active smoking was 34.3%. The outcome of the pregnancy was traced for 288 of the subjects. Cannabis use was associated with a lower gestational age at delivery \( (p < 0.005) \), an increased risk of prematurity \( (p < 0.02) \), and reduction in birth-weight \( (p < 0.002) \). Maternal smoking was associated with a reduction in infant birth-weight \( (p < 0.05) \). This was less pronounced than the effect of other substance misuse\(^{CS422}\). A sample of low-income women attending a prenatal clinic was assessed. The majority of the women decreased their use of cannabis during pregnancy. The assessments of child behavior problems included the Child Behavior Checklist, Teacher’s Report Form, and the Swanson, Noland, and Pelham checklist. Multiple and logistic regressions were employed to analyze the relations between cannabis use and behavior problems of the children at age 10, while controlling for the effects of other extraneous variables. Prenatal cannabis use was significantly related to increased hyperactivity, impulsivity, and inattention symptoms as measured by the Swanson, Noland, and Pelham, increased delinquency as measured by the Child Behavior Checklist, and increased delinquency and externalizing problems as measured by the Teacher’s Report Form. The pathway between prenatal cannabis exposure and delinquency was mediated by the effects of cannabis exposure on inattention symptoms\(^{CS413}\). Attention and impulsivity were assessed using a Continuous Performance Task. Second and third trimester of tobacco exposure and first trimester of cocaine use predicted increased omission errors. Second trimester cannabis use predicted more commission errors and fewer omission errors. There were no significant effects of prenatal alcohol exposure. Lower Stanford-Binet Intelligence Scale composite scores, male gender, and an adult male in the household predicted more errors of commission. Lower Stanford-Binet Intelligence Scale composite scores, younger child age, maternal work/school status, and higher maternal hostility scores predicted more omission errors\(^{CS419}\). The neurophysiological effects of prenatal cannabis exposure on response inhibition were assessed in thirty-one participants aged 18–22. Ottawa Prenatal Prospective Study performed a blocked design Go/No-Go task while neural activity was imaged with functional magnetic resonance imaging. The Ottawa Prenatal Prospective Study is a longitudinal study that provides a unique body of information collected from each participant over 20 years, including prenatal drug history, detailed cognitive/behavioral performance from infancy to young adulthood, and current and past drug usage. The functional magnetic resonance imaging results showed that with increased prenatal cannabis exposure, there was a significant increase in neural activity in bilateral PFC and right premotor cortex during response inhibition. There was also an attenuation of activity in left cerebellum with increased prenatal exposure to cannabis when challenging the response inhibition neural circuitry. Prenatally exposed offspring had significantly more commission errors than non-exposed participants, but all participants were able to perform the task with more than 85% accuracy. The findings were observed when controlling for present cannabis use and prenatal exposure to nicotine, alcohol, and
caffeine, and suggest that prenatal cannabis exposure was related to changes in neural activity during response inhibition that last into young adulthood. The effects of prenatal cannabis and alcohol exposure on school achievement at 10 years of age were examined. Women were interviewed about their substance use at the end of each trimester of pregnancy, at 8 and 18 months, and at 3, 6, 10, 14, and 16 years. The women were of lower socioeconomic status, high school-educated, and light-to-moderate users of cannabis and alcohol. At the 10-year follow-up, the effects of prenatal exposure to cannabis or alcohol on the academic performance of 606 children were assessed. Exposure to one or more cannabis joints per day during the first trimester predicted deficits in Wide Range Achievement Test-Revised reading and spelling scores and a lower rating on the teachers’ evaluations of the children’s performance. This relation was mediated by the effects of first-trimester cannabis exposure on the children’s depression and anxiety symptoms. Second-trimester cannabis use was significantly associated with reading comprehension and underachievement. Exposure to alcohol during the first and second trimesters of pregnancy predicted poorer teachers’ ratings of overall school performance. Second-trimester binge drinking predicted lower reading scores. There was no interaction between prenatal cannabis and alcohol exposure. Each was an independent predictor of academic performance. Pregnant rats were treated daily with Δ9-THC from the fifth day of gestation up to the day before birth (GD21). Then rats were sacrificed and their pups removed for analysis of the neural adhesion molecule L1-mRNA levels in different brain structures. The levels of L1 transcripts were significantly increased in the fimbria, stria terminalis, stria medullaris, corpus callosum, and in gray-matter structures (septum nuclei and the habenula). It remained unchanged in most of the gray-matter structures analyzed (cerebral cortex, BAL nucleus, hippocampus, thalamic and hypothalamic nuclei, basal ganglia, and subventricular zones) and also in a few white-matter structures (fornix and fasciculus retroflexus). The increase in L1-mRNA levels reached statistical significance only in Δ9-THC-exposed males but not females, where only trends or no effects were detected. The results supported evidence on a sexual dimorphism, with greater effects in male fetuses, for the action of cannabinoids in the developing brain. Fetal cannabis exposure has no consistent effect on outcome. Prenatal cocaine exposure has not been shown to have any detrimental effect on cognition, except as mediated through cocaine effects on head size. Although fetal cocaine exposure has been linked to numerous abnormalities in arousal, attention, and neurological and neurophysiological function, most such effects appear to be self-limited and restricted to early infancy and childhood. Opiate exposure elicits a well-described withdrawal syndrome affecting the central nervous, autonomic, and gastrointestinal systems, which is most severe among methadone-exposed infants. Executive functioning in cocaine/polydrug (cannabis, alcohol, and tobacco)-exposed infants was assessed in a single session, occurring between 9.5 and 12.5 months of age. In an A-not-B task, infants searched—after performance-adjusted delays—for an object hidden in a new location. The CE infants did not differ from non-CE controls recruited from the same at-risk population. Comparison of heavier-CE (n = 9) with the combined group of lighter-CE (n = 10) and non-CE (n = 32) infants revealed significant differences on A-not-B performance, as well as on global tests of mental and motor development. Covariates investigated included socioeconomic status, marital status, race, maternal age, years of education,
weeks of gestation, and birth-weight, as well as severity of prenatal cannabis, alcohol, and tobacco exposure. The relationship of heavier-CE status to motor development was mediated by length of gestation, and the relationship of heavier-CE status to mental development was confounded with maternal gestational use of cigarettes. The relationship of heavier-CE status to A-not-B performance remained significant after controlling for potentially confounded variables and mediators, but was not statistically significant after controlling for the variance associated with global mental development. Weight, height, and head circumference were examined in children from birth to early adolescence for whom prenatal exposure to cannabis and cigarettes had been ascertained. The subjects were from a low-risk, predominantly middle-class sample participating in an ongoing longitudinal study. The negative association between growth measures at birth and prenatal cigarette exposure was overcome, sooner in males than females, within the first few years, and by the age of 6 years, the children of heavy smokers were heavier than control subjects. Pre- and postnatal environmental tobacco smoke did not have a negative effect on the growth parameters; however, the choice of bottlefeeding or shorter duration of breastfeeding by women who smoked during pregnancy appeared to play an important positive role in the catch-up observed among the infants of smokers. Prenatal exposure to cannabis was not significantly related to any growth measures at birth, although a smaller head circumference observed at all ages reached statistical significance among the early adolescents born to heavy cannabis users.

Propylspinal myoclonus. A 25-year-old woman with clusters of myoclonus induced by a single exposure to inhaled cannabis was evaluated. Investigations excluded a structural abnormality of the spine. Multichannel surface electromyogram with parallel frontal electroencephalogram recording confirmed the diagnosis of proprio spinal myoclonus.

Prostaglandin synthetase inhibition. Chromatographic fraction of the aerial parts was active on the bull seminal vesicles. Protein synthesis inhibition. Ethanol (95%) extract of the dried resin, administered intraperitoneally to toads at a dose of 10 mg/day for 14 days, was active. The results were significant at p < 0.01 level.

Psoriatic effect. Hot water extract of the dried seed, taken orally by 108 human adults with psoriasis at variable dosage level, was active. After 3–4 weeks of treatment, there was significant improvement. The extract was taken in combination with Rehmannia glutinosa (rhizome), Salvia miltiorrhiza (root), Scrophularia ningpoensis (root), Isatis tinctoria (branch and leaf), Sophora subprostrata (root), Dictamus dasycarpus (rootbark), Polygonum bistorta (rhizome), and Forsythia suspensa (fruit).

Psychosocial morbidity association. Cannabis dependence is a prevalent comorbid substance use disorder among patients early in the course of a schizophrenia-spectrum disorder. Among 29 eligible patients, 18 participated in the study. First-episode patients with comorbid cannabis dependence (n = 8) reported significantly greater childhood physical and sexual abuse compared with those without comorbid cannabis dependence (n = 10). The results indicated the preliminary evidence of an association between childhood maltreatment and cannabis dependence among this especially vulnerable population.

Prolactin inhibition. The dried leaves, smoked by healthy female volunteers at a dose of 1 g/person, produced a decrease in plasma prolactin levels during the luteal phase of the menstrual cycle but not during the follicular phase. The results were significant at p < 0.01 level.
hood physical and sexual abuse may be a risk factor for the initiation of cannabis dependence and other substance use disorders in the early course of schizophrenia. Psychotic effect. Thirty five hundred representatives 19 years of age were examined in a cohort study. The subjects completed a 40-item Community Assessment of Psychic Experiences, measuring subclinical positive (paranoia, hallucinations, grandiosity, first-rank symptoms) and negative psychosis dimensions, depression, and drug use. Use of cannabis was associated positively with both positive and negative dimensions of psychosis, independent of each other and of depression. An association between cannabis and depression disappeared after adjustment for the negative psychosis dimensions. First use of cannabis younger than age 16 years was associated with a much stronger effect than first use after age 15 years, independent of lifetime frequency of use. The association between cannabis and psychosis was not influenced by the distress associated with the experiences, indicating that self-medication may be an unlikely explanation for the entire association between cannabis and psychosis. Cross-sectional epidemiological studies indicated that individuals with psychosis use cannabis more often than other individuals in the general population. It has long been considered that this association was explained by the self-medication hypothesis, postulating that cannabis is used to self-medicate psychotic symptoms. This hypothesis has been recently challenged. Several prospective studies carried out in population-based samples, showed that cannabis exposure was associated with an increased risk of psychosis. A dose–response relationship was found between cannabis exposure and risk of psychosis, and this association was independent from potential confounding factors, such as exposure to other drugs and preexistence of psychotic symptoms. The brain mechanisms underlying the association have to be elucidated; they may implicate deregulation of cannabinoid and dopaminergic systems. Cannabis exposure may be a risk factor for psychotic disorders by interacting with a preexisting vulnerability for these disorders.

Refractory neuropathic pain. Seven patients (three women and four men) aged 60 ± 14 years suffering from chronic refractory neuropathic pain, received oral THC titrated to the maximum dose of 25 mg/day (mean dose: 15 ± 6 mg) during an average of 55.4 days (range: 13–128). Various components of pain (continuous, paroxysmal, and brush-induced allodynia) were assessed using visual analog scale scores. Health-related quality of life was evaluated using the Brief Pain Inventory, and the Hospital Anxiety and Depression scale was used to measure depression and anxiety. THC did not induce significant effect on the various pain, health-related quality of life and anxiety and depression scores. Numerous side effects (notably sedation and asthenia) were observed in five out of seven patients, requiring premature discontinuation of the drug in three patients.

Reproductive effect. Cannabis use during pregnancy in developed nations is estimated to be approx 10%. Recent evidence suggests that the endogenous cannabinoid system, now consisting of two receptors and multiple endocannabinoid ligands, may also play an important role in the maintenance and regulation of early pregnancy and fertility. Drugs of abuse, like alcohol, opiates, cocaine, and cannabis, are used by many young people for their presumed aphrodisiac properties. The opioids inhibit the hypothalamus–pituitary–gonads axis (HPG), and increase the prolactin levels, which interferes with the male and female sexual response. Cannabis, at high doses, could inhibit the HPG axis and reduce fertility. Cannabis initially increases...
libido and potency, but chronic use causes sexual inversion\textsuperscript{364}. Long-term use of cannabis has been found to cause physiological changes that can alter individual reproductive potential. The effects of cannabis depend on the dose and can include death from depression of the respiratory system. Cannabis is absorbed rapidly and eliminated very slowly. Δ-9-THC is highly liposoluble and fixes to the serum proteins, passing to the lungs and liver for metabolization and to the kidneys and liver for excretion. As with estrogens, there is an enterohepatic circuit for reabsorption and elimination. Ninety percent is eliminated in the feces, 65% within 48 hours. Because of the enterohepatic circuit and liposolubility, elimination requires 1 week for completion. The other important biotransformation of the active principle is hydroxylation. The hydroxylated derivatives are responsible for the psychoactivity of cannabis. Cannabis affects both neuroendocrine function and the germ cells. Studies on experimental animals have indicated that THC can cause a decline in the pituitary hormones, follicle stimulating hormone, luteinizing hormone, and prolactin, and in the steroids progesterone, estrogen, and androgens. Human studies have shown that chronic users have decreased levels of serum testosterone. Because steroidogenesis can be restimulated with human chorionic gonadotropin, it appears that THC does not directly affect steroid production by the corpus luteum, but that its action is mediated by the hypothalamus. Because of its potent antigonadotropic action, THC is under study as an anovulatory agent. The same animal studies have shown that ovulation returns to normal 6 months after termination of use. High rates of anovulation and luteal insufficiency have been observed in women smoking cannabis at least three times weekly. THC accumulates in the milk. Animal studies have shown that THC depresses the enzymes necessary for lactation and causes a diminution in the volume of the mammary glands. Significant amounts of the drug have been detected in both mothers’ milk and the blood of newborns. Animal studies indicate that THC crosses the placenta, achieving concentrations in the fetus as high as those in the mother. Animal studies also demonstrated increasing frequency of abortions, intrauterine death, and declines in fetal weight. The effects were probably caused by an alteration in placental function. A human study likewise showed that cannabis use during pregnancy was significantly related to poor fetal development, low birth-weight, diminished size, and decreased cephalic circumference. Congenital malformations have been observed in experimental animals exposed to THC. Declines in sperm volume and count and abnormal sperm motility have been observed in chronic cannabis users. In vitro studies show that THC produces a marked degeneration of human sperm\textsuperscript{365}. Among sexually experienced girls, 39% (n = 123) reported using oral contraceptive pills (OCPs), 5.4% (n = 17) used Depo-Provera® (medroxyprogesterone acetate) or Norplant® (levonorgestrel), and 55.6% (n = 175) used no hormonal method. Logistic regression analysis revealed that the factors most significantly associated with the use of hormonal methods were older age (OR = 1.19; 95% CI, 1.07–1.33), not using a condom at last intercourse (OR = 0.55; CI, 0.34–0.90), and having had a well visit within 1 year (OR = 2.11; CI, 1.12–3.70). OCP users were less likely than Depo-Provera or Norplant users to have used alcohol (p = 0.041), cigarettes (p = 0.002), or cannabis (p = 0.018) in the past 30 days. OCP users were less likely than nonusers of hormonal methods to have smoked cigarettes (p = 0.034) or cannabis (p = 0.052). The school-based clinic had a greater proportion of subjects using long-acting progestins (p < 0.001)\textsuperscript{343}. 
Respiratory effect. Smoking a “joint” of cannabis resulted in exposure to significantly greater amounts of combusted material than with a tobacco cigarette. The histopathological effects of cannabis-smoke exposure included changes consistent with acute and chronic bronchitis. Cellular dysplasia has also been observed, suggesting that, like tobacco smoke, cannabis exposure has the potential to cause malignancy. Symptoms of cough and early morning sputum production are common (20–25%) even in young individuals who smoke cannabis alone. Almost all studies indicated that the effects of cannabis and tobacco smoking are addictive and independent.

A small group of current male cannabis processors with a mean age of 43 years was studied. Questionnaire data, lung function, serial FEV1 and blood were collected from all workers. Seven workers (64%) complained of at least one respiratory symptom (one with byssinosis). The mean percentage predicted FEV1 was 91.5, FVC 97.7, peak expiratory flow 92.1, and forced expiratory flow between 25 and 75% of FVC 79.5. Serial FEV1 measurements in the two workers with work-related respiratory symptoms revealed a mean change in FEV1 on the first working day of −12.9%. This contrasted with +6.25% on the last working day. Respective values for the two workers without work-related symptoms were −1.4 and +3.2%.

Nine hundred forty-three young adults from a birth cohort of 1037 were studied at age 21 years. Standardized respiratory symptom questionnaires were administered. Spirometry and methacholine challenge tests were undertaken. Cannabis dependence was determined using DSM-III-R criteria. Descriptive analyses and comparisons between cannabis-dependent, tobacco-smoking, and nonsmoking groups were undertaken. Adjusted odds ratios for respiratory symptoms, lung function, and airway hyperresponsiveness (PC20) were measured. Ninety-one subjects (9.7%) were cannabis-dependent and 264 (28.1%) were current tobacco smokers. After controlling for tobacco use, respiratory symptoms associated with cannabis dependence included wheezing apart from colds, exercise-induced shortness of breath, nocturnal waking with chest tightness, and early morning sputum production. These were increased by 61, 65, 72 (all \(p < 0.05\)), and 144% (\(p < 0.01\)) respectively, compared with non-tobacco smokers. The frequency of respiratory symptoms in cannabis-dependent subjects was similar to tobacco smokers of 1–10 cigarettes per day. The proportion of cannabis-dependent study members with an FEV1/FVC ratio of less than 80% was 36% compared with 20% for nonsmokers (\(p = 0.04\)). These outcomes occurred independently of coexisting bronchial asthma.

Reversal of cannabinoid addiction. Δ-9-THC was administered orally to mice at a dose of 10 mg/kg twice daily for 6 days to make them dependent on cannabinoids. Other groups of mice were administered orally with a Δ-9-THC and benzoflavone from Passiflora incarnata at doses of 10 or 20 mg/kg twice daily for 6 days. Mice receiving the Δ-9-THC and Passiflora incarnata extract developed significantly less dependence, worse locomotor activity, and less of typical withdrawal effects like paw tremors and headshakes, compared with mice receiving Δ-9-THC alone. Administration of SR-141716A, a selective cannabinoid-receptor antagonist (10 mg/kg, orally), to all groups on the seventh day resulted in an artificial withdrawal. Administration of 20 mg/kg of the Passiflora incarnata benzoflavone moiety to mice showing symptoms of withdrawal owing to administration of SR-141716A produced a marked attenuation of withdrawal effects.

Schizophrenic effect. The nerve growth factor (NGF) serum levels of 109 consecutive drug-naïve schizophrenic patients were
measured and compared with those of healthy controls. The results were correlated with the long-term intake of cannabis and other drugs. Mean (± standard deviation) NGF serum levels of 61 control persons (33.1 ± 31 pg/mL) and 76 schizophrenics who did not consume illegal drugs (26.3 ± 19.5 pg/mL) did not differ significantly. Schizophrenic patients with regular cannabis intake (> 0.5 g per day on average for at least 2 years) had significantly raised NGF serum levels of 412.9 ± 288.4 pg/mL (n = 21) compared with controls and schizophrenic patients not consuming cannabis (p < 0.001). In schizophrenic patients who abused not only cannabis, but also additional substances, NGF concentrations were as high as 2336.2 ± 1711.4 pg/mL (n = 12). On average, heavy cannabis consumers suffered their first episode of schizophrenia 3.5 years (n = 21) earlier than schizophrenic patients who abstained from cannabis. These results indicate that cannabis is a possible risk factor for the development of schizophrenia. This might be reflected in the raised NGF-serum concentrations when both schizophrenia and long-term cannabis abuse prevail.

Schizotypy correlation. Two hundred eleven healthy adults who used cannabis showed higher scores on schizotypy, borderline, and psychoticism scales than never-users. Multivariate analysis, covarying lie scale scores, age, and educational level indicated that high schizotypal traits best discriminated subjects who had used cannabis from never-users, whether or not they reported having used other recreational drugs. The results indicated that cannabis use was related to a personality dimension of psychosis-proneness in healthy people.

Sedative and stimulant effects. A double-blind, placebo-controlled study assessed subjective effects of smoking cannabis with either a long or short breath-holding duration. During eight test sessions, 55 male volunteers made repeated ratings of subjective “high,” sedation, and stimulation, as well as rating their perceptions of motivation and performance on cognitive tests. The long, relative to the short, breath-holding duration increased “high” ratings after smoking cannabis, but not placebo. Cannabis smoking increased sedation and a perception of worsened test performance, and decreased motivation with respect to test performance. Paradoxical subjective effects were observed in those subjects reporting some stimulation, as well as sedation after smoking cannabis, particularly with the long breath-holding duration. Breath-holding duration did not produce any subjective effects that were independent of the drug treatment (i.e., occurred equally after smoking of cannabis and placebo).

Sexual headache. Sexual headaches usually develop during orgasm. The case of a young man and heavy cannabis smoker who suffered posterior cerebral artery infarction during his first episode of coital headache was reported.

Sexual receptivity. The effects of THC on sexual behavior in female rats and its influence on steroid hormone receptors and neurotransmitters in the facilitation of sexual receptivity was examined. Results revealed that the facilitatory effect of THC was inhibited by antagonists to both progesterone and dopamine D(1) receptors. To test further the idea that progesterone receptors (PR) and/or dopamine receptors (D[1]R) in the hypothalamus were required for THC-facilitated sexual behavior in rodents, antisense, and sense oligonucleotides to PR and D(1)R were administered intracerebroventricularly into the third cerebral ventricle of ovariectomized, estradiol benzoate-primed rats. Progesterone- and THC-facilitated sexual behavior was inhibited in animals treated with antisense oligonucleotides to PR or to D(1)R. Antagonists to
cannabinoid receptor-1 subtype (CB1), but not to cannabinoid receptor-2 subtype (CB2) inhibited progesterone- and dopamine-facilitated sexual receptivity in female rats\textsuperscript{240}. Adult female and male rats that had been perinatally exposed to hashish extracts were investigated. Adult males perinatally exposed to hashish extracts exhibited marked changes in the behavioral patterns executed in the sociosexual approach behavior test; these changes did not exist in females. Control males first visited the incentive male and took longer to visit the incentive female, whereas hashish-exposed males followed the opposite pattern. Hashish-exposed males spent more time in the vicinity of the incentive female, whereas they decreased their frequency of visits to, and the time spent in, the male incentive area. This behavior was observed during the first third of the test, but became normalized and even inverted during the last two-thirds. In the social interaction test, the normal reduction in the time spent in active social interaction following the exposure to a neophobic situation (high light levels) in controls did not occur in hashish-exposed males, although these exhibited a response in the dark-light emergence test similar to that of their corresponding controls. No changes were seen in spontaneous locomotor activity in both tests. These behavioral alterations observed in hashish-exposed males were paralleled by a significant decrease in L-3,4-dihydroxyphenylacetic acid contents in the limbic forebrain; this suggests a decreased activity of mesolimbic dopaminergic neurons. No effects were seen in females\textsuperscript{249}.

**Smooth muscle relaxant activity.** Ethanol (95%) and water extracts of the dried aerial parts, at a concentration of 1:1, produced weak activity on the rabbit duodenum. The ethanol extract was equivocal on the guinea pig ileum\textsuperscript{241}. Petroleum ether extract of the dried entire plant, administered intraperitoneally to rats at a dose of 0.89 mg/kg, was active vs corneo-palpebral reflex\textsuperscript{201}.

**Smooth muscle stimulant activity.** Hot water extract of the dried leaf was active on the rabbit and guinea pig intestine\textsuperscript{217}. Water extract of the dried aerial parts at a concentration of 1:1 was equivocal on the guinea pig ileum\textsuperscript{241}.

**Spasticity treatment.** Standardized plant extract was administered orally to 57 MS patients with poorly controlled spasticity, at a dose of 2.5 mg of THC and 0.9 mg of CBD. Patients in group A started with a drug escalation phase from 15 to a maximum of 30 mg of THC by 5 mg per day if well tolerated, being on active medication for 14 days before starting placebo. Patients in group B started with placebo for 7 days, crossed to the active period (14 days), and closed with a three-day placebo period (active drug-dose escalation and placebo sham escalation as in group A). Measures used included daily self-report of spasm frequency and symptoms, Ashworth Scale, Rivermead Mobility Index, 10-meter timed walk, nine-hole peg test, paced auditory serial addition test, and the digit span test. There were no statistically significant differences associated with active treatment compared with placebo, but trends in favor of active treatment were seen for spasm frequency, mobility, and getting to sleep. In the 37 patients (per-protocol set) who received at least 90% of their prescribed dose, improvements in spasm frequency ($p = 0.013$) and mobility after excluding a patient who fell and stopped walking were seen ($p = 0.01$). Minor adverse events were slightly more frequent and severe during active treatment, and toxicity symptoms, which were generally mild, were more pronounced in the active phase\textsuperscript{270}.

Six hundred thirty participants with stable MS and muscle spasticity were treated with oral cannabis extract ($n = 211$), Δ-9-THC ($n = 206$), or placebo ($n = 213$) for 15 weeks. Six hundred eleven of 630 patients were
followed up for the primary end point. No treatment effect of cannabinoids on the primary outcome \( (p = 0.40) \) was noted. The estimated difference in mean reduction in total Ashworth score for participants taking cannabis extract compared with placebo was 0.32 (95% CI, –1.04 to 1.67), and for those taking Δ-9-THC vs placebo it was 0.94 (–0.44 to 2.31). There was an evidence of a treatment effect on patient-reported spasticity and pain \( (p = 0.003) \), with improvement in spasticity reported in 61% \( (n = 121, 95% \text{ CI}, 54.6–68.2) \), 60% \( (n = 108, 52.5–66.8) \), and 46% \( (n = 91, 39–52.9) \) of participants on cannabis extract, Δ-9-THC, and placebo, respectively CS322.

**Spatial working memory effect.** Functional magnetic resonance imaging was used to examine brain activity in 12 long-term heavy cannabis users, 6–36 hours after last use, and in 10 control subjects while they performed a spatial working memory task. Regional brain activation was analyzed and compared using statistical parametric mapping techniques. Compared with controls, cannabis users exhibited increased activation of brain regions typically used for spatial working memory tasks (such as PFC and anterior cingulate). Users also recruited additional regions not typically used for spatial working memory (such as regions in the basal ganglia). The findings remained essentially unchanged when reanalyzed using the subjects ages as a covariate. Brain activation showed little or no significant correlation with subjects years of education, verbal IQ, lifetime episodes of cannabis use, or urinary cannabinoid levels at the time of scanning CS281.

**Spermicidal effect.** Petroleum ether extract of the dried aerial parts at a concentration of 0.74 mmol was active on the human spermatozoa CS186.

**Spontaneous activity reduction.** Petroleum ether extract of the dried entire plant, administered intraperitoneally to guinea pigs at a dose of 100 mg/kg, was active CS022.

**Spontaneous pneumomediastinum.** Spontaneous pneumomediastinum is defined as pneumomediastinum in the absence of an underlying lung disease. It is the second most common cause of chest pain in young, healthy individuals (<30 years) necessitating hospital visits. Inhalational drug use (cocaine and cannabis) has been associated with a significant number of cases, although cases with no apparent etiological or incriminating factors are well-recognized. A case of an 18-year-old high school student with spontaneous pneumomediastinum was evaluated CS421.

**Sudden cardiac death.** An 18-year-old male suffered sudden cardiac death following the use of cocaine, cannabis, and ethanol CS439.

**Sudden infant death syndrome.** In a nationwide case–control study of 369 cases and 1558 controls, two-thirds of SIDS deaths occurred at night (between 10 PM and 7:30 AM). The odds ratio (95% CI) for prone sleep position was 3.86 (2.67–5.59) for deaths occurring at night, and 7.25 (4.52–11.63) for deaths occurring during the day; the difference was significant. The odds ratio for maternal smoking and SIDS deaths occurring at night was 2.28 (1.52–3.42) and for the day, 1.27 (0.79–2.03). If the mother was single, the odds ratio was 2.69 (1.29–3.99) for a nighttime death, and 1.25 (0.76–2.04) for a daytime death. Both interactions were significant. The interactions between time of death and bed sharing, not sleeping in a cot or bassinet, ethnicity, late timing of prenatal care, binge drinking, cannabis use, and illness in the baby were also significant. All were more strongly associated with SIDS occurring at night CS366. In a nationwide case–control study, 393 cases and 1592 controls were analyzed. Adjusting for ethnicity and maternal tobacco use, the SIDS odds ratio for weekly maternal cannabis use since the infant’s birth was 2.23 (95% CI = 1.39, 3.57) compared with nonusers, and the multivariate
odds ratio was 1.55 (95% CI = 0.87, 2.75).

**Suicidal effect.** Standardized interview assessments were conducted with 2311 youths aged 8–15 years who used drugs before age 16. Approximately 15 years after recruitment, 1695 persons (mean age = 21 years) were reassessed. One hundred fifty-five of them made suicide attempts (SA) and 218 had onset of depression-related suicide ideation (SI). The relative risk, from survival analysis and logistic regression models, to study early use of tobacco, alcohol, cannabis, and inhalants, with covariate adjustments for age, sex, race/ethnicity, and other pertinent covariates were examined. Early-onset of cannabis use and inhalant use for females, but not for males, signaled a modest excess risk of SA (cannabis-associated RR = 1.9; *p* = 0.04; inhalant-associated RR = 2.2; *p* = 0.05). Early-onset of cannabis use by females (but not for males) signaled excess risk for SI (RR = 2.9; *p* = 0.006). Early-onset alcohol and tobacco use were not associated with later risk of SA or SI.

Two hundred seventy-seven same-sex twin pairs (median age: 30 years) discordant for cannabis dependence and 311 pairs discordant for early-onset cannabis use (before age 17 years) were examined. Individuals who were cannabis-dependent had odds of SI and SA that were 2.5–2.9 times higher than those of their noncannabis-dependent co-twin. Cannabis dependence was associated with elevated risks of major depressive disorder (MDD) in dizygotic, but not in monozygotic twins. Twins who initiated cannabis use before age 17 years of age had elevated rates of subsequent SA (OR, 3.5, 95% CI, 1.4–8.6) but not of MDD or SI. Early MDD and SI were significantly associated with subsequent risks of cannabis dependence in discordant dizygotic pairs, but not in discordant monozygotic pairs. The results indicated that the comorbidity between cannabis dependence and MDD likely arises through shared genetic and environmental vulnerabilities predisposing to both outcomes. In contrast, associations between cannabis dependence and suicidal behaviors cannot be entirely explained by common predisposing genetic and/or shared environmental predisposition.

**Synergic cytotoxicity.** THC, in A549 lung tumor cells culture at concentrations of less than 5 µg/mL, produced no cytotoxic effect. At higher levels it induced cell necrosis, with a lethal concentration (LC)$_{50}$ of 16–18 µg/mL. Butylated hydroxyanisole ([BHA], a food additive) alone at concentrations of 10–200 µM, produced limited cell toxicity and significantly enhanced the necrotic death resulting from concurrent exposure to THC. In the presence of BHA at 200 µM, the LC$_{50}$ for THC decreased to 10–12 µg/mL. Similar results were obtained with smoke extracts prepared from cannabis cigarettes, but not with extracts from tobacco or placebo cannabis cigarettes (containing no THC). Experiments were repeated in the presence of either diphenyleneiodonium or dicumarol as inhibitors of the redox cycling pathway. Neither of the compounds protected cells from the effects of combined THC and BHA, but rather enhanced necrotic cell death. Measurements of cellular ATP revealed that both THC and BHA reduced ATP levels in A549 cells, consistent with toxic effects on mitochondrial electron transport. The combination was synergistic in this respect, reducing ATP levels to less than 15% of the control. Exposure to cannabis smoke in conjunction with BHA may promote deleterious health effects in the lung.

**Teratogenic activity.** Resin, administered orally to pregnant rabbits at a dose of 1 mL/kg, was active. Alcohol extract of the dried leaves, administered intragastrically to pregnant rats at a dose of 125 mg/kg from days 7 to 16 of gestation, was active. The fetuses showed several gross abnormalities, visceral anomalies, and skeletal malformations. Water extract of the dried
leaf, administered intragastrically to pregnant rats at doses of 125, 200, 400, and 800 mg/kg, produced various types of malformations in the fetuses. Petroleum ether extract of the aerial parts, administered orally to rats and rabbits, was inactive.

**Tourette syndrome.** Tourette syndrome (TS) is a complex inherited disorder of unknown etiology, characterized by multiple motor and vocal tics. Involvement of the central cannabinoid (CB1) system was suggested because of therapeutic effects of cannabis consumption and ∆9-THC treatment in TS patients. The central cannabinoid receptor (CNR1) gene encoding the CNR1 was considered as a candidate gene for TS and systematically screened by single-strand conformation polymorphism analysis and sequencing. Compared with the published CNR1 sequence, three single-base substitutions were identified: 1326T→A, 1359G→A, 1419 + 1G→C. The change at position 1359 is a common polymorphism (1359 G/A) without allelic association with TS. 1326T→A was present in only one TS patient and is a silent mutation, which does not change codon 442 (valine). 1419 + 1G→C affects the first nucleotide immediately following the coding sequence. It was first detected in three of 40 TS patients and none of 81 healthy controls. This statistically significant association with TS (p = 0.034) could not be confirmed in two subsequent cohorts of 56 TS patients (one heterozygous for 1419 + 1G→C) and 55 controls, and 64 patients and 66 controls (one heterozygous for 1419 + 1G→C), respectively. Transcript analysis of lymphocyte RNA from five 1419 + 1G→C carriers revealed no systematic influence on the expression level of the mutated allele. In addition, segregation analysis of 1419 + 1G→C in affected families gave evidence that 1419 + 1G→C does not play a causal role in the etiology of TS. It was concluded that genetic variations of the CNR1 gene are not a plausible explanation for the clinically observed relation between the cannabinoid system and TS. A single-dose, cross-over study in 12 patients, and a 6-week, randomized trial in 24 patients, demonstrated that ∆9-THC, the most psychoactive ingredient of cannabis, reduced tics in TS patients. No serious adverse effects occurred and no impairment on neuropsychological performance was observed. In the randomized, double-blind, placebo-controlled study, 24 patients with TS, according to DSM-III-R criteria, were treated over a 6-week period with up to 10 mg/day of THC. Tics were rated at six visits (visit 1, baseline; visits 2–4, during treatment period; visits 5–6, after withdrawal of medication) using the Tourette Syndrome Clinical Global Impressions scale (TS-CGI), the Shapiro Tourette-Syndrome Severity Scale (STSSS), the Yale Global Tic Severity Scale (YGTSS), the self-rated Tourette Syndrome Symptom List (TSSL), and a videotape-based rating scale. Seven patients dropped out of the study or had to be excluded, but only one because of side effects. Using the TS-CGI, STSSS, YGTSS, and video rating scale, there was a significant difference (p < 0.05) or a trend toward a significant difference (p < 0.1) between THC and placebo groups at visits 2, 3, and/or 4. Using the TSSL at 10 treatment days (between days 16 and 41) there was a significant difference (p < 0.05) between both groups. Analysis of variance also demonstrated a significant difference (p = 0.037). No serious adverse effects occurred. In the randomized, double-blind, placebo-controlled study, the effect of a treatment with up to 10 mg ∆9-THC over a 6-week period on neuropsychological performance in 24 patients suffering from TS was investigated. During medication and immediately, as well as 5–6 weeks after, withdrawal of ∆9-THC treatment, no detrimental effect was seen on learning curve, interference, recall and recognition of word
lists, immediate visual memory span, and divided attention. A trend towards a significant immediate verbal memory span improvement during and after treatment was found. A randomized double-blind placebo-controlled crossover single-dose trial of ∆9-THC (5, 7.5, or 10 mg) in 12 adult TS patients was performed. Tic severity was assessed using the TSSL and examiner ratings (STSSS, YGTSS, TS-CGS). Using the TSSL, patients also rated the severity of associated behavioral disorders. Clinical changes were correlated to maximum plasma levels of THC and its metabolites 11-OH-THC and 11-nor-∆9-tetrahydrocannabinol-9-carboxylic acid. Using the TSSL, there was a significant improvement of tics ($p = 0.015$) and obsessive-compulsive behavior ($p = 0.041$) after treatment with ∆9-THC compared with placebo. Examiner ratings demonstrated a significant difference for the subscore “complex motor tics” ($p = 0.015$) and a trend towards a significant improvement for the subscores “motor tics” ($p = 0.065$), “simple motor tics” ($p = 0.093$), and “vocal tics” ($p = 0.093$). No serious adverse reactions occurred. Five patients experienced mild, transient side effects. There was a significant correlation between tic improvement and maximum 11-OH-THC plasma concentration.

**Toxic effect.** Petroleum ether extract of the dried leaf, administered by gastric intubation to pregnant rats at a dose of 150 mg/kg, produced a reduction of food and water consumption and maternal weight gain. The weight of pups at birth was reduced by approx 10% of the litter size, and pup mortality at birth was not affected significantly. Water extract of the aerial parts, administered intravenously to male adults, was active. The resin, ingested by a 4-year-old girl, showed signs of stupor alternating with brief intervals of excitation and foolish laughing with atactic movements. Her temperature, blood pressure, pulse, hemoglobin, leukocytes, serum electrolytes, and serum urea were normal. Respiratory rate was 12 beats per minute. Blood sugar elevated. Recovery was complete within 24 hours with no treatment. Four patients suffered gastrointestinal disorders and psychological effects after eating salad prepared with hemp seed oil. The concentration of THC in the oil far exceeded the recommended tolerance dose. From January 1998 to January 2002, 213 incidences were recorded of dogs that developed clinical signs following oral exposure to cannabis, with 99% having neurological signs and 30% exhibiting gastrointestinal signs. The cannabis ingested ranged from 0.5 to 90 g. The lowest dose at which signs occurred was 84.7 mg/kg and the highest reported dose was 26.8 g/kg. Onset of signs ranged from 5 minutes to 96 hours, with most signs occurring within 1–3 hours after ingestion. The signs lasted from 30 minutes to 96 hours. Management consisted of decontamination, sedation (with diazepam as drug of choice), fluid therapy, thermoregulation, and general supportive care. All followed animals made full recoveries. The suspension prepared from the benzene washing solution of cannabis seeds, administered intravenously to mice at a dose of 3 mg/kg, produced hypothermia, catalepsy, pentobarbital-induced sleep prolongation, and suppression of locomotor activity. These pharmacological activities of benzene washing solution of cannabis seeds were significantly higher than those of ∆9-THC (3 mg/kg, iv). Ethanol (50%) extract of the entire plant, administered intraperitoneally to mice, produced a maximum tolerated dose of 500 mg/kg.

**Transient global amnesia.** A 6-year-old boy became intoxicated after ingesting cookies laced with cannabis. He was presented with retentive memory deficit of sudden onset that was later diagnosed as
Transient global amnesia. Transient global amnesia owing to cannabis intoxication is an extremely rare event\textsuperscript{CS266}.

**Transient ischemic attack.** A 22-year-old man with a 5-year history of drug and alcohol abuse was presented with a left hemiparesis preceded by three transient ischemic attacks. Two of the attacks occurred while smoking cannabis. Substance abuse was the only identifiable risk factor for the cerebrovascular disease\textsuperscript{CS454}.

**Trauma injuries.** An association between combat-related posttraumatic stress disorder (C-PTSD) and other mental disorders was studied in co-twin (male monozygotic twin pairs in the Vietnam Era Twin Registry). Logistic regression analyses demonstrated that combat exposure, adjusted for C-PTSD, was significantly associated with increased risk for alcohol and cannabis dependence and that C-PTSD mediated the association between combat exposure and both major depression and tobacco dependence\textsuperscript{CS325}. Sera from 111 patients with trauma injuries who presented during a 3-month period were screened for blood alcohol. Urine specimens were analyzed for metabolites of cannabis and cocaine. Sixty-two percent of patients were positive for at least one substance and 20% for two or more. Positivity rates were as follows: cannabis, 46%; alcohol, 32% (with 71% of these having blood alcohol levels >80 mg/dL); and cocaine (6%). Substance usage was most prevalent in the third decade of life. The patients who yielded a positive result were significantly younger than those negatives. There was no significant difference in age or substance usage between the victims of interpersonal violence or road traffic accidents. In the group designated “other accidents,” patients were significantly older and had a lower incidence of substance usage than the other two groups. Cannabis was the most prevalent substance in all groups. Fifty and 55% of victims of road accidents and interpersonal violence, respectively, were positive for cannabis compared with 43 and 27% for alcohol, respectively. There was no significant difference in hospital stay or injury severity score between substance users and non-users\textsuperscript{CS416}.

**Trigeminovascular system effect.** Arachidonyl ethanolamide is believed to be the endogenous ligand of the cannabinoid CB1 and CB2 receptors. Known behavioral effects of AEA are antinociception, catalepsy, hypothermia, and depression of motor activity, similar ∆-9-THC, the psychoactive constituent of cannabis. A role of the CB1 receptor in the trigeminovascular system, using intravital to study the effects of AEA against various vasodilator agents was examined. AEA inhibited dural blood vessel dilation brought about by electrical stimulation by 50%, calcitonin gene-related peptide (CGRP) by 30%, capsaicin by 45%, and NO by 40%. CGRP(8–37) attenuated NO-induced dilation by 50%. The AEA inhibition was reversed by the CB1 receptor antagonist AM251. AEA also reduced the blood pressure changes caused by CGRP injection, this effect was not reversed by AM251\textsuperscript{CS314}.

**Tumor-promoting effect.** A 28-year-old man who abused alcohol, nicotine, and cannabis for several years was investigated. He suffered simultaneously from a squamous cell carcinoma of the hypopharynx with bilateral cervical metastases, an adenocarcinoma of the transverse colon and a primary hepatocellular carcinoma. There were occurrences of three separate malignant tumors with different histologies in the aerodigestive tract, which could be related to a chronic abuse of cannabis\textsuperscript{CS460}.

**Turning behavior.** Cannabinoid agonists: WIN (1–100 ng/mouse), CP-55,940 (0.1–50 ng/mouse), and AEA (0.5–50 ng/mouse), administered unilaterally into the mouse striatum, dose-dependently induced turning
behavior. SR 141716A [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride], the selective antagonist of CB1 receptor, antagonized the three cannabinoid receptor agonists-induced turning with similar effective dose₅₀ (0.13–0.15 mg/kg, intraperitoneally). Spiroperidol (a D2 receptor blocker), (+)-SCH 23390 (a D1 receptor blocker), or prior 6-hydroxydopamine lesions of the striatum blocked WIN- and CP-55,940-induced turning, thus suggesting the involvement of DA transmission in cannabinoid-induced turning.

**Tyrosinase inhibition.** Methanol (80%) extract of the dried aerial parts, at a concentration of 100 µg/mL, produced weak activity.

**Uterine stimulant effect.** Ethanol (50%) extract of the entire plant was inactive on the rat uterus. Ethanol (95%) and water extracts of the dried aerial parts, at a concentration of 1:1, produced strong activity on the non-pregnant rat uterus. Water extract of the flowering tops produced strong activity on the rat uterus.

**Ventricular septal defect.** A Birth Defect Case–Control Study was used to identify 122 isolated simple ventricular septal defect (VSD) cases and 3029 control infants. Exposure data on alcohol, cigarette, and illicit drug use were obtained through standardized interviews with mothers and fathers. Associations between lifestyle factors and VSD were calculated using maternal self-reports; associations were also calculated using paternal proxy reports of the mother’s exposures. Maternal self-report of heavy alcohol consumption and paternal proxy report of the mother’s moderate alcohol consumption were associated with isolated simple VSD. A twofold increase in risk of isolated simple VSD was identified for maternal self- and paternal proxy-reported cannabis use. Risk of isolated simple VSD increased with regular (≥3 days per week) cannabis use for both maternal self- and paternal proxy report, although the association was significant only for maternal self-report.

**Visuospatial memory effect.** Twenty-five college students who were heavy cannabis smokers (who had smoked a median of 29 of the last 30 days) were compared with 30 light smokers (1 day in the last 30 days). The subjects were tested after a supervised period of abstinence from cannabis and other drugs lasting at least 19 hours. Differences between the overall groups of heavy and light smokers did not reach statistical significance on the four subtests of attention administered. On examining data for the two sexes separately, marked and significant differences were found between heavy- and light-smoking women on the subtest examining visuospatial memory. On this test, subjects were required to examine a 6 × 6 “checkerboard” of squares in which certain squares were shaded. The shaded squares were then erased and the subject was required to indicate with the mouse which squares had formerly been shaded. Increasing numbers of shaded squares were presented at each trial. The heavy-smoking women remembered significantly fewer squares on this test, and they made significantly more errors than the light-smoking women. These differences persisted despite different methods of analysis and consideration for possible confounding variables.

**Weight loss.** The dried leaves, administered by gastric intubation to male rats at a dose of 75 mg/kg, was active.

**Wilson’s disease.** A patient with generalized dystonia owing to Wilson’s disease obtained marked improvement in response to smoking cannabis.

**Winiwarter-Buerger disease.** Two young men aged 18 and 20 years with juvenile endarteritis were evaluated. Both developed acute distal ischemia of the lower or upper limbs with arteriographic evidence sugges-
tive of Winiwarter-Buerger disease. Both smoked regularly but not excessively, and both used cannabis regularly. In one case, the therapeutic response to withdrawal of cannabis was good. In the second, use of cannabis continued and arterial disease persisted. The main clinical and radiographical features in this condition are the same as in Winiwarter-Buerger disease CS430.

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