

REVIEW-THEMED ISSUE

The pharmacokinetics and the
pharmacodynamics of cannabinoids

Correspondence Dr Catherine J. Lucas, Hunter Medical Research Institute, Locked Bag 1000, New Lambton, NSW, Australia, 2305. Tel.: +61 (02) 4042 0000; Fax: +61 (02) 4042 0001; E-mail: catherine.lucas@newcastle.edu.au

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Catherine J. Lucas^{1,2,3} , Peter Galettis^{1,2,4}  and Jennifer Schneider^{2,3,5} 

¹Discipline of Clinical Pharmacology, School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia,

²Hunter Medical Research Institute, Newcastle, New South Wales, Australia, ³NSW Health Cannabis Medicines Advisory Service, Newcastle, New South Wales, Australia, ⁴The Australian Centre for Cannabinoid Clinical and Research Excellence, Newcastle, New South Wales, Australia, and

⁵School of Biomedical Sciences and Pharmacy, University of Newcastle, Newcastle, New South Wales, Australia

There is increasing interest in the use of cannabinoids for disease and symptom management, but limited information available regarding their pharmacokinetics and pharmacodynamics to guide prescribers. Cannabis medicines contain a wide variety of chemical compounds, including the cannabinoids delta-9-tetrahydrocannabinol (THC), which is psychoactive, and the nonpsychoactive cannabidiol (CBD). Cannabis use is associated with both pathological and behavioural toxicity and, accordingly, is contraindicated in the context of significant psychiatric, cardiovascular, renal or hepatic illness. The pharmacokinetics of cannabinoids and the effects observed depend on the formulation and route of administration, which should be tailored to individual patient requirements. As both THC and CBD are hepatically metabolized, the potential exists for pharmacokinetic drug interactions via inhibition or induction of enzymes or transporters. An important example is the CBD-mediated inhibition of clobazam metabolism. Pharmacodynamic interactions may occur if cannabis is administered with other central nervous system depressant drugs, and cardiac toxicity may occur via additive hypertension and tachycardia with sympathomimetic agents. More vulnerable populations, such as older patients, may benefit from the potential symptomatic and palliative benefits of cannabinoids but are at increased risk of adverse effects. The limited availability of applicable pharmacokinetic and pharmacodynamic information highlights the need to initiate prescribing cannabis medicines using a 'start low and go slow' approach, carefully observing the patient for desired and adverse effects. Further clinical studies in the actual patient populations for whom prescribing may be considered are needed, to derive a better understanding of these drugs and enhance safe and optimal prescribing.

There is increasing clinical and public interest in using exogenous cannabinoids for disease and symptom management. However, unlike most clinically available drugs, little information on the pharmacokinetics and pharmacodynamics of cannabinoids is available to guide prescribers, and further research is needed to address the major gaps in the knowledge required for optimal prescribing of these medicines.

Most cannabis medicines contain a wide variety of chemical compounds. The primary psychoactive cannabinoid constituent is delta-9-tetrahydrocannabinol (THC) [1, 2], which produces many of the adverse effects reported with cannabis use [3, 4]. Formulations may also contain a high percentage of cannabidiol (CBD), a nonpsychoactive cannabinoid [5, 6] reported to have analgesic [7], neuroprotective

[8], anticonvulsant [1, 6], antiemetic [9], antispasmodic [10] and anti-inflammatory [1, 6, 11] properties.

A variety of standardized, medical-grade cannabis plant-derived or synthetically produced cannabinoid products ('cannabis medicines') have been developed for medicinal use. By contrast, nonmedical-grade products are nonstandardized and contain unknown amounts of THC and CBD [12].

Whereas THC is a partial agonist at the CB1 and CB2 receptors in the endogenous cannabinoid system and exerts its psychoactive and pain modulatory effects via CB1 agonism, CBD has relatively little affinity for the orthostatic sites of these receptors [6, 13] and may inhibit THC binding at CB1 receptors via another mechanism. CBD is also reported to bind to other noncannabinoid receptors [13].

CB1 receptors are mainly located in the central nervous system (CNS) [6, 14] but are also present in the peripheral nervous system, peripheral organs and tissues [6]. CB2 receptors are predominantly expressed in immune tissues [6], and may additionally occur in the CNS [15].

Pharmacokinetics

The pharmacokinetics and the effects observed with cannabis medicines depend on the formulation and route of administration [16–19].

Absorption

Cannabinoids administered via inhalation exhibit similar pharmacokinetics to those administered intravenously [20]. After inhalation, peak plasma concentrations of both THC and CBD are attained rapidly (within 3–10 min) [20, 21] and maximum concentrations are higher relative to oral ingestion [16, 22]. The bioavailability of THC after inhalation reportedly ranges from 10% to 35% [20], attributable to variability (both intra- and intersubject) in inhalational characteristics (number, duration and interval of puffs, breath hold time, inhalation volume), inhalational device [17, 23], size of inhaled particles and site of deposition within the respiratory system [17]. Inhaled CBD was reported to have an average systemic bioavailability of 31%, and a plasma concentration–time profile similar to that of THC [20, 21].

Smoking is the most common route of administration of recreational cannabis [16]. Maximum THC concentration and area under the curve (AUC) were observed to be greater in frequent smokers relative to occasional smokers, which is likely to be due to more efficient smoking by frequent smokers [16, 18].

Using a vaporizer to administer cannabinoid compounds avoids the respiratory risks associated with smoking cannabis, and exposure to toxic pyrolytic compounds formed via combustion [24]. The pharmacokinetics of vaporized and smoked cannabinoids are comparable [16].

Inhalational or oromucosal delivery of cannabinoids avoids or reduces the extensive first-pass metabolism observed following oral cannabinoid administration.

Oromucosal preparations [e.g. Sativex® (nabiximols) oromucosal spray] undergo rapid absorption via the oral mucosa (and hence are useful for symptoms requiring rapid relief), producing plasma drug concentrations higher relative to oral, but reduced relative to inhaled THC [25]. However, part of the dose may be swallowed and orally absorbed [25].

THC and CBD are both highly lipophilic and have poor oral bioavailability (estimated to be as low as 6%) [26, 27]. Oral THC formulations exhibit variable absorption and undergo extensive hepatic first-pass metabolism [28], resulting in lower peak plasma THC concentration relative to inhalation [29] and a longer delay (~120 min) to reach peak concentration [20, 30]. Following oral administration of CBD, a similar plasma concentration–time profile to that of oral THC has been observed [20]. Based on this profile, oral formulations may be useful for patients requiring symptomatic relief over a longer period.

Transdermal administration of cannabinoids avoids first-pass metabolism but their extremely hydrophobic nature limits diffusion across the aqueous layer of the skin [31]. Effective skin transport can only be obtained by permeation enhancement [32].

In vitro studies with human skin have determined the permeability of CBD to be 10-fold higher than that of delta-9-THC and delta-8-THC (less potent but more stable relative to delta-9-THC) [31, 33], consistent with CBD being relatively less lipophilic [33].

Following the application of a transdermal patch to hairless guinea pigs (with a permeability coefficient of delta-8-THC comparable with that of human skin), the delta-8-THC steady-state plasma concentration reached 4.4 ng ml⁻¹ within 1.4 h and was maintained for ≤48 h [34]. Absorption from patches, influenced by factors including local blood flow and skin permeability, may be impaired in cachectic relative to normal-weight subjects [35]. Although transdermal administration is currently not used clinically, it is of potential future utility in the context of nausea, vomiting and anorexia.

Distribution

Cannabinoids rapidly distribute into well-vascularized organs (e.g. lung, heart, brain, liver) [26, 29, 36], with subsequent equilibration into less vascularized tissue [36]. Distribution may be affected by body size and composition, and disease states influencing the permeability of blood–tissue barriers [37].

With chronic use, cannabinoids may accumulate in adipose tissues [22, 38]. Subsequent release and redistribution [22] (e.g. in the context of weight loss) [39] may result in the persistence of cannabinoid activity for several weeks post-administration [23, 26, 40, 41].

The volumes of distribution (*V*_d) of CBD and THC are high [respectively, *V*_{dβ} ~32 l kg⁻¹ (calculated following intravenous administration) [21] and *V*_{dss} 3.4 l kg⁻¹ (calculated following inhaled administration)] [22].

Metabolism

The metabolism of THC is predominantly hepatic, via cytochrome P450 (CYP 450) isozymes CYP2C9, CYP2C19 and CYP3A4. THC is mainly metabolized to 11-hydroxy-THC (11-OH-THC) and 11-carboxy-THC (11-COOH-THC), which undergoes glucuronidation [42] and is subsequently excreted in the faeces and urine [26, 28]. Metabolism also occurs in extra-hepatic tissues that express CYP450, including the small intestine and brain [22]. The metabolite 11-OH-THC is reported to have psychoactive activity [43].

Importantly, lipophilic THC is able to cross the placenta [30] and is excreted in human breast milk [44] – raising concern for toxicity to the developing brain.

CBD is also hepatically metabolized, primarily by isozymes CYP2C19 and CYP3A4 and additionally, CYP1A1, CYP1A2, CYP2C9 and CYP2D6 [45]. After hydroxylation to 7-hydroxy cannabidiol (7-OH-CBD), there is further hepatic metabolism and subsequent faecal, and, to a lesser extent, urinary, excretion of those metabolites [26].

Little is known about the pharmacological activity of the metabolites of CBD in humans [46].

Elimination

Estimates of the elimination half-life of THC vary [20]. A population pharmacokinetic model has described a fast initial half-life (approximately 6 min) and long terminal half-life (22 h) [47], the latter influenced by equilibration between lipid storage compartments and the blood [37].

A relatively longer elimination half-life is observed in heavy users [18], attributable to slow redistribution from deep compartments such as fatty tissues [18, 19]. Consequently, THC concentrations $>1 \mu\text{g l}^{-1}$ may be measurable in the blood of heavy users more than 24 h following the last cannabis use [18, 48, 49].

CBD has also been reported to have a long terminal elimination half-life, with the average half-life following intravenous dosing observed to be 24 ± 6 h and post-inhalation to be 31 ± 4 h [21]. An investigation of repeated daily oral administration of CBD elicited an elimination half-life ranging from 2 to 5 days [50].

Potential interactions

Dose–response and drug–drug interaction information is lacking [23].

Potential exists for pharmacokinetic interactions between both THC and CBD and other drugs, via inhibition or induction of enzymes [26, 38, 40, 51] or transporters and additionally, pharmacodynamic drug–drug interactions.

Both cannabis and tobacco smoking induce CYP1A2, and the induction is additive when they are smoked together [52]. This may be significant in a patient coadministered a drug metabolized by CYP1A2.

There are case reports of mania resulting from coadministration of cannabis with fluoxetine [53] (potentially CYP2D6 mediated), and of delirium and hypomania with disulfiram [54, 55] (mechanism unelucidated).

An *in vitro* study reported that CBD significantly inhibits P-glycoprotein-mediated drug transport, suggesting that CBD could potentially influence the absorption and disposition of other coadministered drugs [56]. Coadministration of rifampicin (a CYP3A4 inducer) significantly reduced peak plasma concentrations of CBD, while coadministration of the CYP3A4 inhibitor ketoconazole nearly doubled peak plasma drug concentrations [57].

In vitro, CBD was observed to be a potent inhibitor of CYP2C19 enzymes [58]. Accordingly, clinicians should bear in mind the potential for drug interactions to occur. For example, clobazam is converted by CYP3A4 to its active metabolite, N-desmethylclobazam, which is subsequently converted by CYP2C19 to an inactive metabolite [59]. The causal benefit of CBD in reducing convulsive seizure frequency, reported in a randomized controlled trial of cannabidiol for Dravet syndrome [60], is difficult to ascertain, given that CBD-mediated inhibition of clobazam metabolism has been demonstrated to result in an up to eight-fold increase in clobazam concentration [61]. Adverse events increased in the CBD vs. placebo group (including somnolence, lethargy and fatigue) [60] could potentially be attributable to increased concentrations of clobazam and N-desmethylclobazam [23].

Pharmacodynamics

Cannabis produces sedation, and significant pharmacodynamic interactions may occur if it is administered with other CNS depressant drugs (such as sedatives or hypnotics), via potentiation of central effects [62]. In human volunteers, ethanol was found to increase plasma THC levels and the subjective effect of smoked cannabis [63].

Cannabis use is associated with both pathological and behavioural toxicity [64–66]. Contraindications to cannabinoid therapies include significant psychiatric, cardiovascular, renal or hepatic illness [25]. THC produces dose-dependent performance impairment [18]. Following a single inhaled dose of THC, impairment was greatest during the first hour postdose and declined over the following 2–4 h [19]. Substantial cognitive and psychomotor impairment is associated with blood THC concentrations in excess of 5 ng ml^{-1} [67]. In healthy volunteers, administration of THC produced psychotic symptoms, altered perception, increased anxiety and cognitive deficits [68]. Cannabinoids may induce tachycardia [69], probably via direct agonism of CB1 receptors in cardiac tissue [70]. Cardiac toxicity may occur via additive hypertension and tachycardia with amphetamines, cocaine, atropine or other sympathomimetic agents [71, 72].

Coadministration of CBD has been reported to reduce THC-associated adverse psychotropic and cardiovascular effects (tachycardia) [73].

CBD has been reportedly associated with fatigue and somnolence [60], potentially compounded by coadministration with CNS-active medications.

Cannabis with high THC content is associated with a greater severity of addiction relative to cannabis with low THC content [74].

A large, nationally representative sample of US adults determined that the lifetime cumulative probability of transitioning from cannabis use to dependence was 8.9%, with increased risk of transition to dependence conferred by history of psychiatric or substance dependence comorbidity [75].

In general, currently available pharmacokinetic and pharmacodynamic data were obtained from studies in healthy volunteers, or cannabis users. Pharmacokinetic data derived from such studies cannot simply be extrapolated to more vulnerable patient groups or the cannabis-naïve population. Patient-specific variables influencing cannabinoid pharmacokinetics may include history of cannabis use, pharmacogenetics, body size and composition, disease state, diet, microbiome and additional unknown factors [23].

There are limited data regarding the efficacy and safety of cannabis use in older subjects [1]. This population may benefit from its potential symptomatic and palliative benefits but, in the context of comorbidity, polypharmacy and increased cognitive vulnerability, is predisposed to more severe manifestations of adverse effects such as sedation, with a resultant increased risk of falls [1]. Pharmacokinetic parameters influenced by age, such as reduced hepatic and renal clearance, and relative increases in body fat [76] and, consequently, V_d , can result in an increased bioavailability of THC and prolongation of half-life [1].

For most cannabinoid formulations, there are limited data pertaining to their pharmacokinetic profiles, which are likely

to demonstrate both inter- and inpatient variability [23]. Caution must be exercised in extrapolating data between different routes of administration and formulations, the selection of which should be tailored depending on individual patient requirements.

The limited availability of applicable pharmacokinetic and pharmacodynamic information highlights the need to initiate the prescription of cannabis medicines using a 'start low and go slow' approach, carefully observing the patient for desired and adverse effects. It is only through further clinical studies, collecting pharmacokinetic and pharmacodynamic data in the actual patient population for whom prescribing may be considered, that a better understanding of these drugs will be achieved, enhancing safe and optimal prescribing.

Competing Interests

There are no competing interests to declare.

References

- van den Elsen GA, Ahmed AI, Lammers M, Kramers C, Verkes RJ, van der Marck MA, *et al.* Efficacy and safety of medical cannabinoids in older subjects: a systematic review. *Ageing Res Rev* 2014; 14: 56–64.
- Kauert GF, Ramaekers JG, Schneider E, Moeller MR, Toennes SW. Pharmacokinetic properties of delta9-tetrahydrocannabinol in serum and oral fluid. *J Anal Toxicol* 2007; 31: 288–93.
- Atakan Z. Cannabis, a complex plant: different compounds and different effects on individuals. *Ther Adv Psychopharmacol* 2012; 2: 241–54.
- Kogan NM, Mechoulam R. Cannabinoids in health and disease. *Dialogues Clin Neurosci* 2007; 9: 413–30.
- Russo EB, McPartland JM. Cannabis is more than simply delta(9)-tetrahydrocannabinol. *Psychopharmacology (Berl)* 2003; 165: 431–2.
- McCarberg BH, Barkin RL. The future of cannabinoids as analgesic agents: a pharmacologic, pharmacokinetic, and pharmacodynamic overview. *Am J Ther* 2007; 14: 475–83.
- Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA* 2003; 290: 1757–62.
- Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (–) delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci USA* 1998; 95: 8268–73.
- Rock EM, Bolognini D, Limebeer CL, Cascio MG, Anavi-Goffer S, Fletcher PJ, *et al.* Cannabidiol, a non-psychoactive component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT(1A) somatodendritic autoreceptors in the dorsal raphe nucleus. *Br J Pharmacol* 2012; 165: 2620–34.
- Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Huffman JW, *et al.* Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature* 2000; 404: 84–7.
- Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andrekos E, Mechoulam R, *et al.* The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritis therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci USA* 2000; 97: 9561–6.
- Belackova V, Ritter A, Shanahan M, Chalmers J, Hughes C, Barratt M, *et al.* Medicinal cannabis in Australia – framing the regulatory options. Sydney: Drug Policy Modelling Program 2015. Available at https://ndarc.med.unsw.edu.au/sites/default/files/ndarc/resources/DPMP%20Medicinal%20Cannabis%20Paper%2010th%20March%202015_0.pdf (last accessed 30 July 2018).
- Laprairie RB, Bagher AM, Kelly MEM, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB(1) receptor. *Br J Pharmacol* 2015; 172: 4790–805.
- Onaivi ES, Ishiguro H, Gong JP, Patel S, Perchuk A, Meozzi PA, *et al.* Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain. *Ann N Y Acad Sci* 2006; 1074: 514–36.
- van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, *et al.* Identification and functional characterization of brainstem cannabinoid CB2 receptors. *Science* 2005; 310: 329–32.
- Newmeyer MN, Swortwood MJ, Barnes AJ, Abulseoud OA, Scheidweiler KB, Huestis MA. Free and glucuronide whole blood cannabinoids' pharmacokinetics after controlled smoked, vaporized, and oral cannabis administration in frequent and occasional cannabis users: identification of recent cannabis intake. *Clin Chem* 2016; 62: 1579–92.
- Solowij N, Broyd SJ, van Hell HH, Hazekamp A. A protocol for the delivery of cannabidiol (CBD) and combined CBD and 9-tetrahydrocannabinol (THC) by vaporisation. *BMC Pharmacol Toxicol* 2014; 15: 58.
- Toennes SW, Ramaekers JG, Theunissen EL, Moeller MR, Kauert GF. Comparison of cannabinoid pharmacokinetic properties in occasional and heavy users smoking a marijuana or placebo joint. *J Anal Toxicol* 2008; 32: 470–7.
- Johansson E, Noren K, Sjoval J, Halldin MM. Determination of delta 1-tetrahydrocannabinol in human fat biopsies from marijuana users by gas chromatography-mass spectrometry. *Biomed Chromatogr* 1989; 3: 35–8.
- Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003; 42: 327–60.
- Ohlsson A, Lindgren JE, Andersson S, Agurell S, Gillespie H, Hollister LE. Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration. *Biomed Environ Mass Spectrom* 1986; 13: 77–83.
- Huestis MA. Human cannabinoid pharmacokinetics. *Chem Biodivers* 2007; 4: 1770–804.
- Martin JH, Schneider J, Lucas CJ, Galettis P. Exogenous cannabinoid efficacy: merely a pharmacokinetic interaction? *Clin Pharmacokinet* 2018; 57: 539–45.
- Gieringer D, St. Laurent S, Goodrich S. Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds. *J Cannabis Ther* 2004; 1: 7–27.
- Therapeutic Goods Administration. Australian public assessment report for nabiximols. Available at <https://www.tga.gov.au/sites/default/files/auspar-nabiximols-130927.pdf> (last accessed 10 July 2017).
- Gaston TE, Friedman D. Pharmacology of cannabinoids in the treatment of epilepsy. *Epilepsy Behav* 2017; 70 (Pt B): 313–8.

- 27 Agurell S, Carlsson S, Lindgren JE, Ohlsson A, Gillespie H, Hollister L. Interactions of delta 1-tetrahydrocannabinol with cannabidiol and cannabidiol following oral administration in man. Assay of cannabidiol and cannabidiol by mass fragmentography. *Experientia* 1981; 37: 1090–2.
- 28 Eichler M, Spinedi L, Unfer-Grauwiler S, Bodmer M, Surber C, Luedi M, *et al.* Heat exposure of *Cannabis sativa* extracts affects the pharmacokinetic and metabolic profile in healthy male subjects. *Planta Med* 2012; 78: 686–91.
- 29 Dinis-Oliveira RJ. Metabolomics of delta9-tetrahydrocannabinol: implications in toxicity. *Drug Metab Rev* 2016; 48: 80–7.
- 30 Huestis MA. Pharmacokinetics and metabolism of the plant cannabinoids, delta9-tetrahydrocannabinol, cannabidiol and cannabiol. *Handb Exp Pharmacol* 2005; 657–90.
- 31 Challapalli PV, Stinchcomb AL. *In vitro* experiment optimization for measuring tetrahydrocannabinol skin permeation. *Int J Pharm* 2002; 241: 329–39.
- 32 Lodzki M, Godin B, Rakou L, Mechoulam R, Gallily R, Touitou E. Cannabidiol-transdermal delivery and anti-inflammatory effect in a murine model. *J Control Release* 2003; 93: 377–87.
- 33 Stinchcomb AL, Valiveti S, Hammell DC, Ramsey DR. Human skin permeation of Delta8-tetrahydrocannabinol, cannabidiol and cannabiol. *J Pharm Pharmacol* 2004; 56: 291–7.
- 34 Valiveti S, Hammell DC, Earles DC, Stinchcomb AL. *In vitro/in vivo* correlation studies for transdermal delta 8-THC development. *J Pharm Sci* 2004; 93: 1154–64.
- 35 Heiskanen T, Matzke S, Haakana S, Gergov M, Vuori E, Kalso E. Transdermal fentanyl in cachectic cancer patients. *Pain* 2009; 144: 218–22.
- 36 Hunt CA, Jones RT. Tolerance and disposition of tetrahydrocannabinol in man. *J Pharmacol Exp Ther* 1980; 215: 35–44.
- 37 Lucas CJ, Galettis P, Song S, Solowij N, Reuter SE, Schneider J, *et al.* Cannabinoid disposition after human intraperitoneal use: an insight into intraperitoneal pharmacokinetic properties in metastatic cancer. *Clin Ther* 2018; <https://doi.org/10.1016/j.clinthera.2017.12.008>.
- 38 Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, *et al.* Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* 2014; 55: 791–802.
- 39 Gunasekaran N, Long LE, Dawson BL, Hansen GH, Richardson DP, Li KM, *et al.* Reintoxication: the release of fat-stored delta(9)-tetrahydrocannabinol (THC) into blood is enhanced by food deprivation or ACTH exposure. *Br J Pharmacol* 2009; 158: 1330–7.
- 40 Rosenberg EC, Tsien RW, Whalley BJ, Devinsky O. Cannabinoids and epilepsy. *Neurotherapeutics* 2015; 12: 747–68.
- 41 Zhornitsky S, Potvin S. Cannabidiol in humans – the quest for therapeutic targets. *Pharmaceuticals (Basel)* 2012; 5: 529–52.
- 42 Schwowe DM, Karschner EL, Gorelick DA, Huestis MA. Identification of recent cannabis use: whole-blood and plasma free and glucuronidated cannabinoid pharmacokinetics following controlled smoked cannabis administration. *Clin Chem* 2011; 57: 1406–14.
- 43 Lemberger L, Crabtree RE, Rowe HM. 11-hydroxy-9-tetrahydrocannabinol: pharmacology, disposition, and metabolism of a major metabolite of marijuana in man. *Science* 1972; 177: 62–4.
- 44 Perez-Reyes M, Wall ME. Presence of delta9-tetrahydrocannabinol in human milk. *N Engl J Med* 1982; 307: 819–20.
- 45 Zundulka O, Dovrtelova G, Noskova K, Turjap M, Sulcova A, Hanus L, *et al.* Cannabinoids and cytochrome P450 interactions. *Curr Drug Metab* 2016; 17: 206–26.
- 46 Ujváry I, Hanuš L. Human metabolites of cannabidiol: a review on their formation, biological activity, and relevance in therapy. *Cannabis Cannabinoid Res* 2016; 1: 90–101.
- 47 Heuberger JA, Guan Z, Oyetayo OO, Klumpers L, Morrison PD, Beumer TL, *et al.* Population pharmacokinetic model of THC integrates oral, intravenous, and pulmonary dosing and characterizes short- and long-term pharmacokinetics. *Clin Pharmacokinet* 2015; 54: 209–19.
- 48 Skopp G, Potsch L. Cannabinoid concentrations in spot serum samples 24–48 hours after discontinuation of cannabis smoking. *J Anal Toxicol* 2008; 32: 160–4.
- 49 Johansson E, Halldin MM, Agurell S, Hollister LE, Gillespie HK. Terminal elimination plasma half-life of delta 1-tetrahydrocannabinol (delta 1-THC) in heavy users of marijuana. *Eur J Clin Pharmacol* 1989; 37: 273–7.
- 50 Consroe P, Laguna J, Allender J, Snider S, Stern L, Sandyk R, *et al.* Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacol Biochem Behav* 1991; 40: 701–8.
- 51 Ibeas Bih C, Chen T, Nunn AV, Bazet M, Dallas M, Whalley BJ. Molecular targets of cannabidiol in neurological disorders. *Neurotherapeutics* 2015; 12: 699–730.
- 52 Anderson GD, Chan LN. Pharmacokinetic drug interactions with tobacco, cannabinoids and smoking cessation products. *Clin Pharmacokinet* 2016; 55: 1353–68.
- 53 Stoll AL, Cole JO, Lukas SE. A case of mania as a result of fluoxetine-marijuana interaction. *J Clin Psychiatry* 1991; 52: 280–1.
- 54 Mackie J, Clark D. Cannabis toxic psychosis while on disulfiram. *Br J Psychiatry* 1994; 164: 421.
- 55 Lacoursiere RB, Swatek R. Adverse interaction between disulfiram and marijuana: a case report. *Am J Psychiatry* 1983; 140: 243–4.
- 56 Zhu HJ, Wang JS, Markowitz JS, Donovan JL, Gibson BB, Gefroh HA, *et al.* Characterization of P-glycoprotein inhibition by major cannabinoids from marijuana. *J Pharmacol Exp Ther* 2006; 317: 850–7.
- 57 Stott C, White L, Wright S, Wilbraham D, Guy G. A phase I, open-label, randomized, crossover study in three parallel groups to evaluate the effect of rifampicin, ketoconazole, and omeprazole on the pharmacokinetics of THC/CBD oromucosal spray in healthy volunteers. *Springerplus* 2013; 2: 236.
- 58 Jiang R, Yamaori S, Okamoto Y, Yamamoto I, Watanabe K. Cannabidiol is a potent inhibitor of the catalytic activity of cytochrome P450 2C19. *Drug Metab Pharmacokinet* 2013; 28: 332–8.
- 59 Russell GR, Phelps SJ, Shelton CM, Wheless JW. Impact of drug interactions on clobazam and N-desmethyloclobazam concentrations in pediatric patients with epilepsy. *Ther Drug Monit* 2018; 40: 452–62.

- 60 Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, *et al.* Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med* 2017; 376: 2011–20.
- 61 Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia* 2015; 56: 1246–51.
- 62 Arellano AL, Papaseit E, Romaguera A, Torrens M, Farre M. Neuropsychiatric and general interactions of natural and synthetic cannabinoids with drugs of abuse and medicines. *CNS Neurol Disord Drug Targets* 2017; 16: 554–66.
- 63 Lukas SE, Orozco S. Ethanol increases plasma delta(9)-tetrahydrocannabinol (THC) levels and subjective effects after marijuana smoking in human volunteers. *Drug Alcohol Depend* 2001; 64: 143–9.
- 64 Andreasson S, Allebeck P, Rydberg U. Schizophrenia in users and nonusers of cannabis. A longitudinal study in Stockholm County. *Acta Psychiatr Scand* 1989; 79: 505–10.
- 65 Schoeler T, Monk A, Sami MB, Klamerus E, Foglia E, Brown R, *et al.* Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. *Lancet Psychiatry* 2016; 3: 215–25.
- 66 Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. *Am J Cardiol* 2014; 113: 187–90.
- 67 Hartman RL, Huestis MA. Cannabis effects on driving skills. *Clin Chem* 2013; 59: 478–92.
- 68 D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, *et al.* The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* 2004; 29: 1558–72.
- 69 Karschner EL, Darwin WD, McMahon RP, Liu F, Wright S, Goodwin RS, *et al.* Subjective and physiological effects after controlled Sativex and oral THC administration. *Clin Pharmacol Ther* 2011; 89: 400–7.
- 70 Dumont GJ, Kramers C, Sweep FC, Touw DJ, van Hasselt JG, de Kam M, *et al.* Cannabis coadministration potentiates the effects of 'ecstasy' on heart rate and temperature in humans. *Clin Pharmacol Ther* 2009; 86: 160–6.
- 71 Benowitz NL, Jones RT. Prolonged delta-9-tetrahydrocannabinol ingestion. Effects of sympathomimetic amines and autonomic blockades. *Clin Pharmacol Ther* 1977; 21: 336–42.
- 72 Foltin RW, Fischman MW, Pedroso JJ, Pearson GD. Marijuana and cocaine interactions in humans: cardiovascular consequences. *Pharmacol Biochem Behav* 1987; 28: 459–64.
- 73 Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses* 2006; 66: 234–46.
- 74 Freeman TP, Winstock AR. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. *Psychol Med* 2015; 45: 3181–9.
- 75 Lopez-Quintero C, Perez de los Cobos J, Hasin DS, Okuda M, Wang S, Grant BF, *et al.* Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend* 2011; 115: 120–30.
- 76 Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013; 381: 752–62.