Erratum

Erratum to cannabis in palliative care: current challenges and practical recommendations

Claude Cyr[1], Maria Fernanda Arboleda[2,3], Sunil Kumar Aggarwal[4], Lynda G. Balneaves[5], Paul Daeninck[6], Andrée Néron[7], Erin Prosk[3], Antonio Vigano[2,3]

[1]Department of Family Medicine, [2]Department of Oncology, McGill University, Montreal, Canada; [3]Clinique Santé Cannabis, Montreal, Canada; [4]Department of Rehabilitation Medicine, Department of Geography, University of Washington, Seattle, WA, USA; [5]College of Nursing, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada; [6]Department of Family Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada; [7]Pharmacy Department, CHUM (Centre Hospitalier de l'Université de Montréal), Montreal, Canada

Correspondence to: Claude Cyr, MD. Clinique La Cité Médicale de Montréal, 3500 Boulevard DeMaisonneuve west, suite 1520, Montreal, QC, H3Z 3C1, Canada. Email: claudecyrmd@gmail.com.

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Cannabis in palliative care: current challenges and practical recommendations

The authors of this article would like to make some corrections in two sections as some omissions and errors were unfortunately overlooked during the editing process. Some additional pharmacological details have also been included, and may be of use for clinicians who wish to delve deeper into these issues.

Challenge Section 5: what is clinically relevant from the scientific literature on the pharmacology of cannabinoids including metabolism and for potential drug-drug interactions?

In this section, warfarin is mentioned as a potent CYP 3A4 inhibitor when in fact it has little or no influence on 3A4. Rather, the cited article points to a possible interaction between cannabidiol (CBD) in its "therapeutic" form and warfarin. This anecdotal reaction is caused by cannabidiol's inhibitory effect on CYP 2C9, which increases warfarin's effect (1).

Cannabidiol is a substrate of the hepatic cytochrome P-450 system and several isoforms are involved in its transformation (CYP 3A4 and CYP 2C19 predominantly and CYP1A1, CYP1A2, CYP2C9, CYP2D6, CYP3A5 secondarily) (1-7). Cannabidiol is also an important metabolic inhibitor of several CYPs and may even auto-inhibit its own metabolism. Therapeutic doses of isolated CBD may therefore influence the elimination of other drugs administered concomitantly. Furthermore, the sequence in which drugs are initiated can also influence the outcome (adding cannabis to an existing drug regimen versus adding a drug to a stable dose of cannabis). However, in clinical practice, one must keep in mind that drug interactions are complex mechanisms that do not necessarily produce serious clinical consequences for the patient even if the interaction is considered pharmacologically significant (1,4). According to the current state of knowledge, this is probably the case with cannabinoids, at least and when using smaller dose ranges that are generally recommended in most clinical conditions.

Furthermore, many factors influence serum concentrations of a particular drug, including CYP activities and their genetic polymorphisms, epigenetic changes, and other exogenous factors. These factors influence the metabolic activity of CYP substantially and are a major source of variability in pharmacokinetics and in the response of individuals to drugs (2,4,5). Also, there is a known discrepancy in the literature between drug interactions resulting from direct experimental observations and those found after systemic drug administration in individuals. While some preclinical studies have shown clear effects by direct interaction, the same substances do not necessarily produce a notable effect after systemic administration.

Exposure time is another factor affecting the results of interaction studies. After repeated drug exposures, plasma and

tissue concentrations rise to higher levels than after a single dose. It has also been observed that reciprocal exchanges occur between cannabinoids and cannabinoid receptors, which could lead to changes in signaling and regulatory mechanisms of hepatic cytochromes (5,6). Although much has been observed over the last 30 years concerning the effects and metabolic fate of cannabinoids, many questions remain unanswered.

Inter-species differences in CYP systems create an important barrier for evaluating interactions in clinical settings. Data can be obtained from animals, *in vitro*, *in vivo*, *ex vivo*, after a single or multiple doses. This makes for a complex risk evaluation with every individual patient. However, results from most preclinical studies on drug interactions with delta-9 THC and CBD match their corresponding *in vitro* experiments. Consequently, cannabinoids are now generally regarded as cytochrome inhibitors (2,4-6).

Cannabinoids have emerged as a powerful drug class for the treatment of inflammatory and autoimmune diseases due to their immunosuppressive properties. Significant clinical and experimental data on their use as anti-inflammatory agents exist in many autoimmune disease settings, and some interesting studies with cannabidiol are underway, evaluating their potential role in transplant rejection (current clinical trials, phase II studies). Clinicians must, therefore, be very cautious as cannabidiol, a potent inhibitor of CYP 3A4 (and P-glycoprotein inhibitor—*in vitro* and *in vivo* studies) may very well impact on cyclosporine and tacrolimus metabolism (8-10).

The distinction between cannabis in its smoked form versus oral form also needs to be pointed out. The potential interactions with cannabis smoke are similar to those for tobacco, which implies a possible interaction with CYP 1A2. Polycyclic aromatic hydrocarbons are probably to blame for this effect (2,3,6). Clozapine, duloxetine and theophylline are examples of substrates that could undergo induction interaction and thus lose their effectiveness if the patient is a persistent smoker (monitor consumption ≥2 joints/week) (4).

In summary, there is currently little evidence-based data on how to manage the use of cannabis with other drugs. For the time being, frail patients or those with polypharmacy issues should be advised that delta-9 THC and cannabidiol may result in drug interactions that may impact the efficacy and safety of their other medications.

Challenge 8: what is considered a safe approach for dose initiation and titration

Again, we would like to clarify and modulate our statement on the concept of the lethal dose of cannabis. This issue remains very controversial, as cannabis has a historically wide margin of safety (11). For obvious ethical reasons, we do not have experimental studies to determine the lethal dose in humans and the few reported cases of fatalities with cannabis use often involve individuals who have used the inhaled form and suffered from multiple comorbidities, including cardiovascular conditions (11). Recently, however, the unexpected deaths of two otherwise healthy young men prompted Hartung *et al.* to suggest that smoked cannabis may have caused fatal cardiovascular complications. However, the blood levels of THC in these individuals were considered to be in the low range, which suggests that the cause of death would less likely be caused by an overdose of THC.

Animal studies as well as clinical studies conducted with approved cannabinoid drugs reveal a low risk of toxicity. Indeed, the virtual absence of CB receptors in the respiratory center in the brainstem explains this safety margin. This data is reassuring when using cannabis at therapeutic doses and with standardized formulations used for medical purposes. However, when side effects are considered, the risk assessment for cannabis and drugs of abuse is often poorly characterized (anecdotal cases, subjective impressions, animal studies) as opposed to data obtained for registered drugs or other consumer products. Thus, the most important pitfall in our knowledge with substances of abuse (including cannabis), is the lack of dose-response toxicology data in humans (12).

Consequently, the lethal half dose (LD50) for THC in humans which has been estimated to be around 30 mg/kg, remains under scrutiny (13). If this were truly the case, however, we must take caution with the rapid emergence of concentrated THC extracts known as “wax”, “dabs”, or “butane hash oil” which can contain up to 80% THC; one tenth of an ounce of these products can contain 2000 mg of THC (13). Lachenmeier *et al.* reported another method for comparative risk assessment of drugs using the margin of exposure (MOE) approach. The MOE is defined as the ratio between the toxicological threshold (benchmark dose) and estimated human intake. Median lethal dose values from animal experiments were used to derive the benchmark dose. Human intake was calculated for individual scenarios and population-based scenarios, with cannabis having an estimated MOE >10,000 (12).

Finally, we recommend that clinicians remain aware that, in contrast with regulated medical cannabis and synthetic

cannabinoids approved by the pharmaceutical industry, there exists a parallel market providing untested medical cannabis products that may produce unpredictable effects. This is especially the case for untested CBD-only products that have actually been shown to contain varying amounts of THC. Furthermore, when using supraphysiologic doses of therapeutic cannabis products, the endocannabinoid system may become overloaded that can provoke hazardous side effects, including acute psychosis, anxiety attacks, hypotension and even syncope and falls. The recent arrival of pure synthetic cannabinoid agonists (K2, Spice) are up to 100 times more powerful than natural THC and much more harmful than cannabis even at smaller doses. They are often consumed by youth to foil drug testing or because they are perceived to be harmless derivatives of a natural product. Thousands of cases of acute toxicity are reported annually with these unregulated products (12,14).

We regret the error and any inconvenience it might have caused.

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