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Product Review

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CANNabinoid Drug Interaction Review (CANN-DIR™)

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Abstract
Non-prescription cannabidiol (CBD) and medical marijuana (cannabis) currently do not have US Food and Drug Administration (FDA)-approved prescribing information nor a dedicated resource to evaluate potential cannabinoid drug-drug interactions with other medications. The CANNabinoid Drug Interaction Review (CANN-DIR™) is a free web-based platform that has been developed to screen for potential drug-drug interactions from the perspective of how a cannabinoid delta-9-tetrahydrocannabinol (THC), CBD, or a combination of THC/CBD may affect the metabolism of another prescribed medication. CANN-DIR™ is based on FDA-approved prescribing information for the prescription cannabinoids (dronabinol, nabilone, nabiximols, and prescription CBD) and other FDA-approved prescribing information for medications sharing similar metabolic enzymes (e.g., the FDA "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers"). The Summary of Product Characteristics (SmPC) was the source of drug-drug interaction information for the combined Δ^9-THC & CBD product nabiximols (Sativex®). CANN-DIR™ provides an expeditious review of cannabinoid drug-drug interaction information, and also a platform from which the patient and health care provider can print out the search results to either initiate a conversation, or for the health care provider to provide a written information sheet to supplement their verbal discussion. Additionally, to more effectively reach a global audience, the end user of CANN-DIR™ has the ability to currently navigate and print results in any of the following ten languages: Chinese, English, French, German, Nepali, Polish, Russian, Spanish, Swedish, and Vietnamese.

Introduction

As prescription cannabidiol (CBD) and non-prescription CBD oil, recreational and medical marijuana (cannabis), and other prescription cannabinoids (dronabinol, nabilone, nabiximols) are increasingly being used, there is the risk of unintended drug-drug interactions (DDIs) [1]. These potential DDIs should not be simply

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Fig. 1. CANN-DIR™ QR Code.

limited to the dizziness, somnolence, or confusion when co-administered with other sedating medications but from the perspective of how various cannabinoids may affect the metabolism of other prescription medications co-administered by the patient. Specifically, the co-administration of any cannabinoid with a prescription medication has the potential to interfere with the metabolism of the prescription medication and therefore alter blood levels. Recognizing the opportunity to increase patient safety by reducing unintended DDIs, we have developed the CANNabinoid Drug Interaction Review (CANN-DIR™) as a free digital resource to highlight potential DDIs.

CANNabinoid Drug Interaction Review (CANN-DIR™)

CANN-DIR™ is a digital evolution of the authors' prior work entitled "*Delta-9-tetrahydrocannabinol and Cannabidiol Drug-Drug Interactions. Medical Cannabis and Cannabinoids*" [2]. CANN-DIR™ was developed to screen for potential DDIs from the perspective of how a cannabinoid delta-9-tetrahydrocannabinol (THC), CBD, or a combination of THC/CBD may affect the metabolism of another concomitantly prescribed medication. CANN-DIR™ is freely accessible at the following URL https://CANN-DIR.psu.edu or its QR code (Fig. 1).

Medication Reconciliation Platform

Medication reconciliation is the formal process of developing the most accurate list of medications a patient is taking to further evaluate their pharmacodynamic and pharmacokinetic interactions [3]. The January 2020 Joint Commission (TJC) National Patient Safety Goals® continues to focus on the medication reconciliation performance element (NPSG.03.06.01) in both the ambulatory health care [4] and the hospital [5] programs as a means of enhancing patient safety. Potential DDIs are not just limited to prescription medications but can also occur with other concomitantly taken herbal medications, over the counter medications, supplements, and now the increasingly available cannabinoids. It is important to develop a comprehensive and accurate medication list along with the medication's corresponding, dose, frequency, route of administration, and medical indication to further reduce adverse events that can be attributed to DDIs, especially during transitions of care [6].

CANN-DIR™ provides a platform from which written medication information can be provided. A patient/caregiver can search how the cannabinoid of interest may affect other concomitantly prescribed medications, print this information, and provide to their health care provider for further discussion. Likewise, the health care provider can perform this same process and provide a written document to supplement their patient consultation in any of the ten languages currently supported. It is anticipated that supplementing verbal instructions with this written information will help improve patient outcomes and improve patient safety [7].

Languages

This latest iteration of CANN-DIR™ was translated from English into additional nine languages: Chinese, French, German, Nepali, Polish, Russian, Spanish, Swedish, and Vietnamese. These languages were selected because they are the most commonly spoken at our Penn State Health clinics and hospitals along with the languages of countries from which CANN-DIR™ was viewed. We plan to include additional languages in future iterations.

Demographics

Before a search begins, CANN-DIR™ has a de-identified one-time demographics page that allows the user to self-identify as either being a "Health Care Professional,"

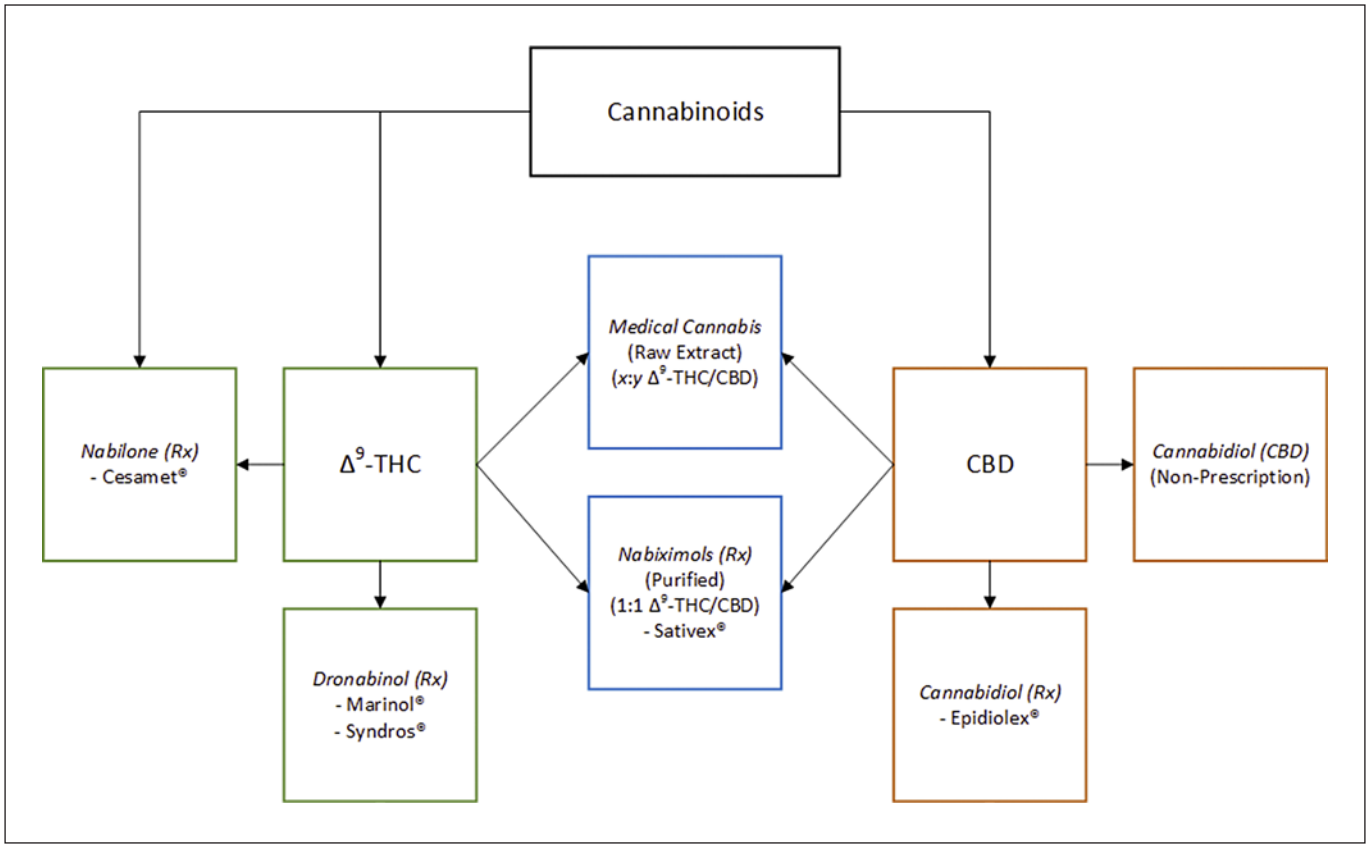


Fig. 2. Δ^9-THC and CBD cannabinoid (prescription, OTC, and medical cannabis) formulations. This figure taken with permission from the author's prior work titled: 'Delta-9-Tetrahydrocannabinol and Cannabidiol Drug-Drug Interactions' [2]. OTC, over the counter.

"Patient/Caregiver," or the opportunity to "Prefer Not to Identify." This provides the authors an opportunity to tailor future iterations to a more specific audience and to assess knowledge base and gaps [8]. At the time of this publication, CANN-DIR™ has been viewed in 36 countries. We also created the CANN-DIR@psu.edu email address with which the end user can communicate with our team.

Cannabinoid (PRECIPITANT) Medications

CANN-DIR™ is based on three broad categories of cannabinoids: delta-9-tetrahydrocannabinol (THC), CBD, or a combination of THC/CBD as illustrated in Figure 2 [2]. The US Food and Drug Administration (FDA) approved prescribing information served as the initial reference to DDI information for dronabinol (Marinol® [9], Syndros® [10]); delta-9-tetrahydrocannabinol (THC); nabilone (Cesamet®) [11]; and CBD (Epidiolex®) [12]. The Summary of Product Characteristics (SmPC) was the source of DDI information for the combined Δ^9-THC and CBD product nabiximols (Sativex®) [13].

CANN-DIR™ provides an opportunity to choose "THC," "CBD," or "THC/CBD" as the cannabinoid (PRECIPITANT) medication of interest (Fig. 3). The "THC" category comprised the delta-9-tetrahydrocannabinol therapeutic class composed of dronabinol (Marinol®, Syndros®) and nabilone (Cesamet®) prescription medications. The "CBD" category comprised non-prescription CBD oil and the prescription CBD (Epidiolex®). Lastly, the "THC/CBD" category comprised THC/CBD mixtures such as recreational cannabis use, medical marijuana extracts, or nabiximols (Sativex®) a medication that is available in other countries, but currently an investigational product in the USA.

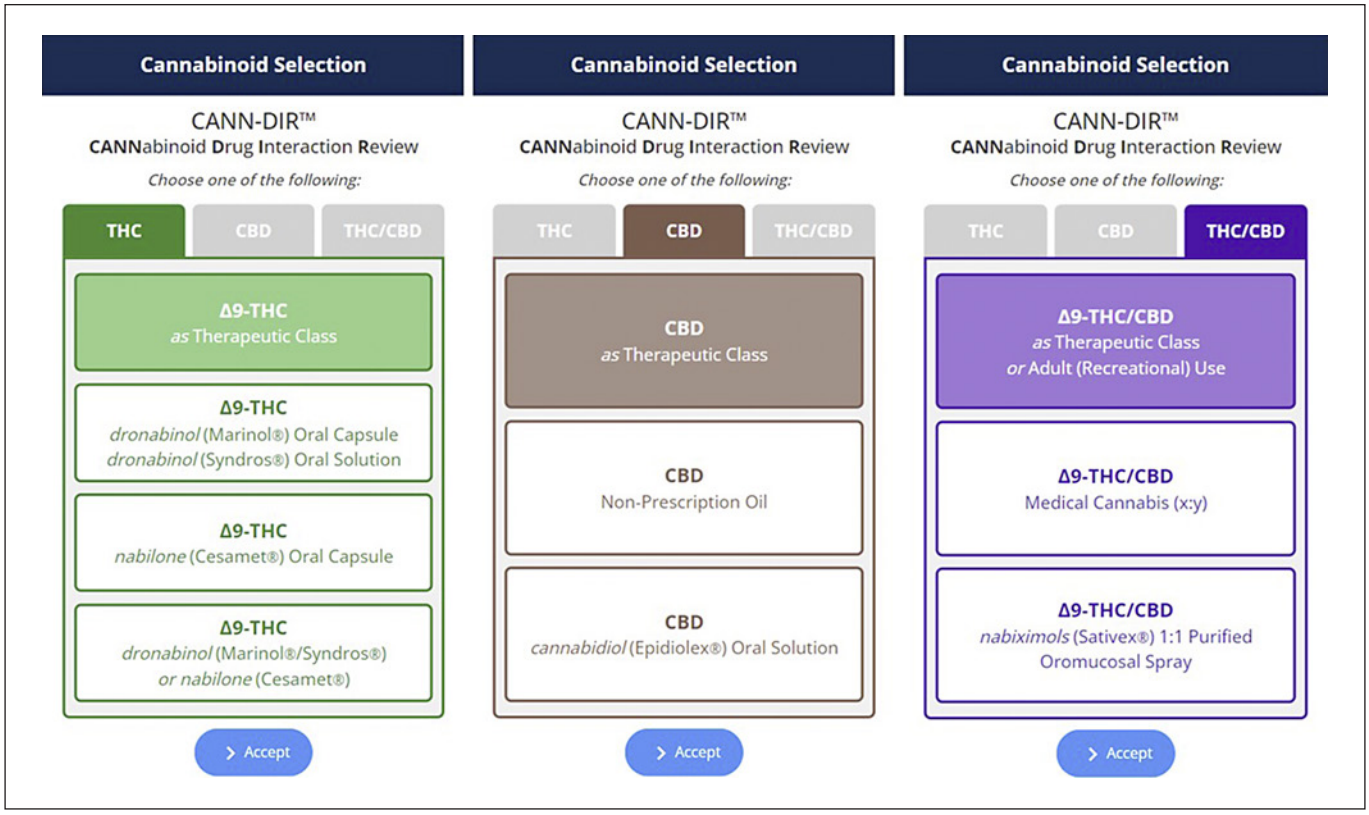


Fig. 3. Screens depicting cannabinoid selection for THC, CBD, or the combination of THC/CBD.

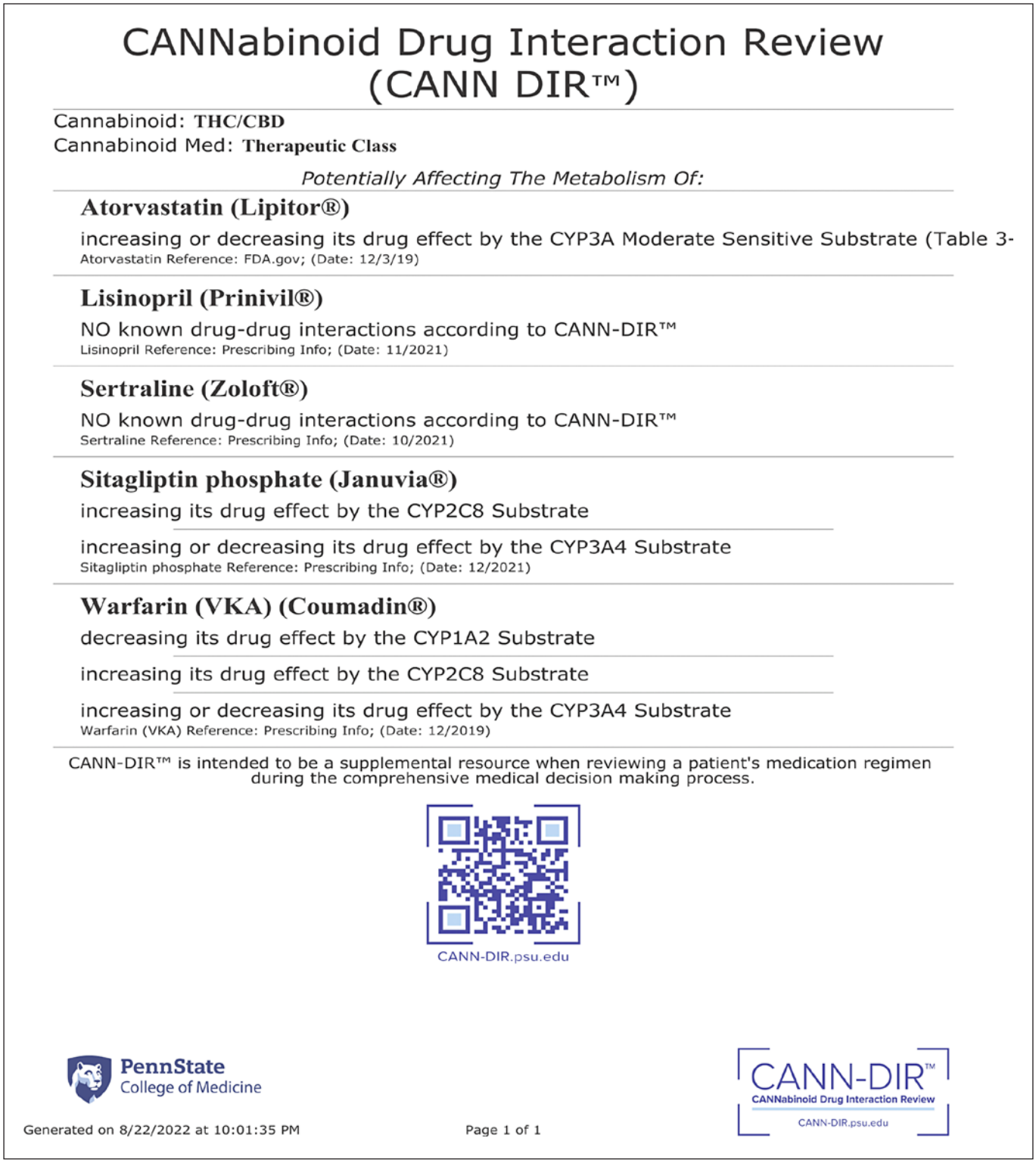
Database (OBJECT) Medications

In order to assure a comprehensive list of medications, whether there is a potential DDI identified at this time or not, the drug database contained within CANN-DIR™ comprised medications listed in the US FDA document "*Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers*" [14]. This list of medications was further supplemented using FDA-approved prescribing information based on the Agency for Healthcare Research and Quality (AHRQ) list of the top 225 most commonly prescribed medications in the USA in 2018 [15]. In addition, the drug database contained within CANN-DIR™ contains commonly prescribed oral oncology, oral HIV, oral antiepileptic medications, as well as the recent Emergency Use Authorized (EUA) oral medications (ritonavir-boosted nirmatrelvir and molnupiravir) to treat COVID-19.

Results

CANN-DIR™ lists the OBJECT medications in alphabetical order by generic name along with its corresponding brand name. Either the generic or brand name can be used to search for potential DDIs. CANN-DIR™ permits the end user to save the other OBJECT medications of interest so that they can be evaluated with a THC, CBD, or THC/CBD cannabinoid of interest without having to input the medications repeatedly.

The drug interaction results screen lists the cannabinoid (PRECIPITANT) medication that has no DDI or either inhibits, induces, or competes as a substrate for a specific enzyme/receptor for the OBJECT medications of interest. The results also include a URL directing to detailed information on the cannabinoid or other medication of interest. The results screen can also be printed from a downloaded PDF as illustrated in Figure 4.



CANNabinoid Drug Interaction Review (CANN DIR™)

Cannabinoid: **THC/CBD**

Cannabinoid Med: **Therapeutic Class**

Potentially Affecting The Metabolism Of:

Atorvastatin (Lipitor®)

increasing or decreasing its drug effect by the CYP3A Moderate Sensitive Substrate (Table 3-

Atorvastatin Reference: FDA.gov; (Date: 12/3/19)

Lisinopril (Prinivil®)

NO known drug-drug interactions according to CANN-DIR™

Lisinopril Reference: Prescribing Info; (Date: 11/2021)

Sertraline (Zoloft®)

NO known drug-drug interactions according to CANN-DIR™

Sertraline Reference: Prescribing Info; (Date: 10/2021)

Sitagliptin phosphate (Januvia®)

increasing its drug effect by the CYP2C8 Substrate

increasing or decreasing its drug effect by the CYP3A4 Substrate

Sitagliptin phosphate Reference: Prescribing Info; (Date: 12/2021)

Warfarin (VKA) (Coumadin®)

decreasing its drug effect by the CYP1A2 Substrate

increasing its drug effect by the CYP2C8 Substrate

increasing or decreasing its drug effect by the CYP3A4 Substrate

Warfarin (VKA) Reference: Prescribing Info; (Date: 12/2019)

CANN-DIR™ is intended to be a supplemental resource when reviewing a patient's medication regimen during the comprehensive medical decision making process.

CANN-DIR.psu.edu

PennState College of Medicine

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Page 1 of 1

CANN-DIR™ CANNabinoid Drug Interaction Review CANN-DIR.psu.edu

Fig. 4. Printed CANN-DIR™ drug interaction results screen.

Conclusion

CANN-DIR™ is the only known DDI web-based platform specific to the cannabinoid class of medications. This online tool provides a free publicly accessible mechanism by which a health care provider, caregiver, or patient can determine if there is a potential DDI between a cannabinoid medication and other prescription medications. If such a potential DDI is identified, it does not necessarily mean that it is a contraindicated combination nor a clinically significant interaction but an opportunity to evaluate the combination or adjust the dose of either the cannabinoid or concomitantly prescribed medication. CANN-DIR™ provides a readily accessible DDI resource for the patient and health care provider that can be navigated in several different languages. This platform also provides the patient and health care provider an opportunity to print out their results to either initiate a conversation or provide written documentation supplementing a consultation.

CANN-DIR™ is intended to be an adjunct in decision-making since individual patient characteristics (e.g., gender, age, genomic profile, ethnicity, hepatic function, renal function, and disease state) for the medically complex patient should also be taken into account. In the time since CANN-DIR™ was deployed (March 2022), it has already undergone planned updates to keep the medication database current, along with software code enhancements. At this time, we have completed a v2.0.3 update and have a planned v3 update for the Spring of 2023.

Limitations

By design, this web-based URL platform does not evaluate DDIs from the perspective of how a medication (e.g., warfarin) affects the cannabinoid, nor does it make explicit predictions of the outcome of potential DDIs. Currently, CANN-DIR™ provides DDI results written for the health care provider; however, future iterations will have a more patient-focused results section when the "Patient/Caregiver" button is selected.

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Conflict of Interest Statement

K.E.V. and the Penn State College of Medicine are the recipients of research support from PA Options for Wellness (a state-approved medical marijuana clinical registrant). The funding source had no involvement in the writing or analysis of work presented, nor the decision of what to present.

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Author Contributions

Paul T. Kocis and Kent E. Vrana substantially contributed to the conception and design of the work; drafted the work and revised it critically for important intellectual content; was involved in the final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Samuel Wadrose, Ryan Lee Wakefield, Aqib Ahmed, Renata Calle, and Rohan Gajjar substantially contributed to the design of the work; revised the work critically for important intellectual content; was involved in the final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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