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Assessing the accuracy and deficits of popular drug-interaction software programs in detecting interactions between cannabis and pharmaceutical drugs

Nathan C. Ramsbacher
University of Montana, Missoula, nr225605@umconnect.umt.edu

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By

Nathan Ramsbacher, PharmD Candidate 2022

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Abstract

- **Purpose** – The management of drug interactions in healthcare is a large concern for pharmacists and other healthcare professionals, especially for patients requiring large amounts of medications. Healthcare professionals and patients alike utilize drug-interaction software programs (DISPs) frequently to manage medications and make clinical decisions. There is a large discrepancy between DISPs in terms of detecting clinically significant drug interactions. Notably, cannabis does not flag as an interaction as reliably as pharmaceutical drugs on many DISPs. With rising cannabis use in the United States, patients deserve to make decisions on how to safely use cannabis with their prescription drugs which may depend on the accuracy of DISPs.
- **Methods** – First, I made a literature review table of 30 interactions between cannabis and pharmaceutical drugs (18 true interactions, 12 false). Next, I entered each interaction pair into eight individuals DISPs and noted if it was captured or not. After this, I calculated the inter-rater reliability between the DISPs to assess how much agreement there was between them. I then calculated the specificity, sensitivity, and accuracy of each DISP.
- **Significance** – Overall, DISPs did not have a high "agreeance" on what was detected as a true drug interaction with cannabis; Fleiss kappa was very low at k=0.216 (95% CI = 0.148, 0.284), where scores range from -1 to 1 with "1.000" being high agreement. Average accuracy of detecting a drug interaction with cannabis was somewhat low (76.2%), where DISPs tailored for healthcare professionals far outperformed DISPs tailored for the layperson. There is a notable disparity between the sensitivity of DISPs with the lowest score being 44.4% and the highest being 100%. A lower sensitivity equates to missing clinically important interactions which may result in negative health outcomes. Healthcare professionals and patients should recognize the importance of drug interactions with cannabis and should utilize DISPs that most accurately reflect drug interactions with cannabis.

1.Introduction

Drug-interaction software programs (DISPs) are widely used by the medical community to detect clinically significant interactions that could affect healthcare. In general, some are intended to be used by healthcare professionals while others are geared towards the layperson. Drug-drug interactions (DDIs) can lead to higher/lower serum levels of drugs that could result in higher morbidity/mortality for unsuspecting patients. DISPs have a known variability in their capacity to detect clinically significant DDIs.[1,2] The variance in accuracy may again lead to higher morbidity/mortality by inability to detect clinically significant DDIs.

Although previous research has studied the variability between DISPs, none thus far have examined its implications to cannabis-drug interactions. Cannabis is not always recognized as a clinically significant DDI by patients or by healthcare professionals. Although clinical research is somewhat lacking for DDIs with cannabis, many DDIs are known.[3-9] With rising cannabis use in the United States, patients deserve to make decisions on how to safely use cannabis with their prescription drugs which may depend on the accuracy of DISPs. Thus, this study sought to explore the accuracy of popular DISPs in detecting DDIs between prescription medications and cannabis as well as the inter-rater reliability between DISPs to measure how well each program "agreed" with one another that a DDI was captured or not. This was accomplished by measuring the sensitivity, specificity, overall accuracy, and Fleiss' kappa score.

2.Methods

2a. Creating a literature review table

To begin, a literature review table was created consisting of various cannabis-drug interactions. The list of potential drug interactions was generated from several literature reviews looking at drug interactions with cannabis including drugs specific to pain management, oncology, and neurology.[3-7] To assess accuracy, some drug interactions were "true" (a verified DDI) and some were "false" (random drug pairs or DDIs that were questionably true). Each DDI pair had literature to support its rationale as a "true" or "false" DDI which was categorized by type of study. This ultimately made the basis for whether a DDI was considered potentially clinically significant and defined a "true" DDI. The literature review table then was the "gold standard" to compare each DISP to.

2b. Evaluating individual DISPs

Next, each DDI pair was entered into eight different DISPs. Each DISP was chosen due to their popularity with healthcare professionals as well as the public. Using the search terms, "cannabis", "cannabidiol", and "dronabinol", drug interaction pairs were captured with each program. Following, a table was created that compared the literature review table to what was captured with each DISP. If the program captured the interaction correctly (true positive or true negative), it was colored green. If the program captured the interaction incorrectly (false positive or false negative), it was colored red.

2c. Sensitivity, Specificity, Overall Accuracy, and Inter-Rater Reliability

Statistics were calculated using IBM SPSS Statistics Data Editor version 18 for Windows (https://www.ibm.com/marketplace/cloud/statistical-analysis-and-reporting/us/en-us). To capture inter-rater reliability to assess how well each DISP "agreed" with each other, Fleiss' kappa was calculated with an asymptotic confidence interval. Fleiss kappa was calculated using 30 cases (individual DDIs), 2 categories (DDI captured – yes or no), and 8 raters (DISPs). SPSS then calculated sensitivity, specificity, and overall accuracy using the formulas:

- Sensitivity = # True Positives / (# True Positives + # False Negatives)
- Specificity = # True Negatives / (# True Negatives + # False Positives)
- Overall accuracy = Sensitivity * Prevalence + Specificity x (1-Prevalance)

Clopper-Pearson confidence intervals were also captured for sensitivity, specificity, and accuracy scores.

3.Results

(See below)

ID#	Cannabis-Drug Interaction	Mechanism/rationale	Type of Study*	Level of Evidence**	Potentially clinically significant drug interaction? (1 = yes = "true" DDI, 0 = no = "false" DDI)	For "false" DDIs: was the DDI theoretical and proven false (=3) or randomly generated having no theoretical or clinically significant DDIs (=4)?
1	Acetaminophen	Mice that were CBD doses followed by a challenge with APAP experienced significant hepatotoxicity, resulting from modulation of different UGT and CYP enzymes by CBD.[11]	8	6	0	3
2	Alcohol (ethyl alcohol)	Ethanol may increase the absorption of cannabis and subjective effects.[12]	3	1b	1	n/a
		Ethanol and cannabis combination vs ethanol alone contributed more deleterious effects on psychomotor performance.[13]	3	1b	1	n/a
3	Buprenorphine	Cannabis users had 2.7-fold higher concentrations of buprenorphine compared to non-users.[14]	4	4	1	n/a
4	Carvedilol	n/a	n/a	n/a	0	4
5	Chlorpromazine	CYP1A2 induction by cannabis resulted in 50% more clearance of chlorpromazine.[15]	4	2b	1	n/a
6	Citalopram	Inhibition of CYP3A4 and 2C19 by CBD significantly increased citalopram concentrations but it was unclear whether it was associated with an increase in major adverse events.[16]	2	2a	1	n/a
7	Clobazam	Serum levels of the active metabolite of clobazam (N-desmethylclobazam) were increased in children and adults with increasing CBD doses.[17]	4	2b	1	n/a
8	Clopidogrel	CBD is a potent inhibitor of 2C19 in vivo.[18]	8	6	1	n/a
9	Clozapine	CYP1A2 induction by smoking resulted in 2.5 times lower concentrations of clozapine compared to non-smokers.[19]	4	2b	1	n/a
10	Codeine	Cannabis may potentially increase morphine potency; dose reduction may be required.[20]	9	5	1	n/a
11	Dabigatran	n/a	n/a	n/a	0	4
12	Diazepam	Diazepam is primary metabolized by CYP2C19 and 3A4.[21]	4	2b	1	n/a
		CBD is a potent inhibitor of 2C19 in vivo.[18]	8	6	1	n/a

13	Docetaxel	Coadministration of cannabis and irinotecan or docetaxel did not significantly increase serum levels of the irinotecan or docetaxel in 24 patients over 3 weeks.[22]	4	2b	0	3
14	Flecainide	n/a	n/a	n/a	0	4
15	Fluvastatin	n/a	n/a	n/a	0	4
16	Indinavir	CYP3A4 inhibition/induction by cannabis decreased Cmax of indinavir, although it did not impact antiretroviral efficacy.[23]	3	1b	1	n/a
17	Irinotecan	Coadministration of cannabis and irinotecan or docetaxel did not significantly increase serum levels of the irinotecan or docetaxel in 24 patients over 3 weeks.[22]	4	2b	0	3
18	Metoprolol	n/a	n/a	n/a	0	4
19	Morphine	Cannabis may potentially increase morphine potency due to downregulation of UGT2B7; dose reduction may be required.[20]	9	5	1	n/a
20	Omeprazole	CBD is a potent inhibitor of CYP2C19 in vivo.[18]	8	6	1	n/a
		Omeprazole is a major metabolite of CYP2C19.[24]	3	1b	1	n/a
21	Oxycodone	Cannabis may potentially increase oxycodone potency due to inhibition/downregulation of CYP3A4/5, CYP2D6, UGT2B7, and UGT2B4; dose reduction may be required.[20]	9	5	1	n/a
22	Phenytoin	CBD is a potent inhibitor of CYP2C19 in vivo.[18]	8	6	1	n/a
		Phenytoin is a major substrate of CYP2C19 in vivo.[25]	3	1b	1	n/a
23	Pravastatin	n/a	n/a	n/a	0	4
24	Rosiglitazone	n/a	n/a	n/a	0	4
25	Rosuvastatin	n/a	n/a	n/a	0	4
26	Theophylline	Theophylline clearance increased in chronic marijuana smokers almost 1.5x fold.[26]	4	2b	1	n/a
27	Tizanidine	Tizanidine is primarily metabolized by CYP1A2.[27]	8	6	1	n/a
		Cannabis is a strong inducer of CYP1A2.[9]	2	2a	1	n/a
28	Topiramate	Serum levels of topiramate were increased in children and adults with increasing CBD doses but were within therapeutic range.[17]	4	2b	1	n/a

29	Warfarin	Coadministration of warfarin and increasing CBD doses resulted in clinically significant increased INR.[28]	6	4	1	n/a
		In vitro analysis using human liver microsomes revealed that THC, CBD, and CBM inhibited CYP2C9.[29]	8	6	1	n/a
30	Zonisamide	Serum levels of zonisamide were increased in adults with increasing CBD doses but were within therapeutic range.[17]	4	2b	0	3

Table 1. *Drug-interaction pairs found*

**For Type of Study, 1 = meta-analysis, 2 = systematic review, 3 = RCT, 4 = cohort study, 5 = case control, 6 = case series/case report, 7 = expert opinion, 8 = animal research or in vitro, 9 = review article*

***For Level of Evidence, 1a = systematic review of RCTs, 1b = individual RCTs, 2a = systematic review of cohort studies, 2b = individual cohort study/low quality RCT, 3a = systematic review of case controls, 3b = individual case controls, 4 = case series or low-quality cohort/case controls, 5 = expert opinions, 6 = N/A*

ID #	Cannabis-Drug Interaction	Actual List - "Gold Standard" (1 = true DDI, 0 = false DDI)	UpToDate	Micromedex	Medscape	WebMD	Drugs.com	DrugBank Online	Natural Medicines	Facts and Comparisons
1	Acetaminophen	0	0	0	0	0	1	1	0	0
2	Alcohol (ethyl alcohol)	1	1	1	1	1	1	1	1	1
3	Buprenorphine	1	1	1	1	1	1	1	1	0
4	Carvedilol	0	0	0	1	1	1	0	0	0
5	Chlorpromazine	1	1	1	1	1	1	1	1	0
6	Citalopram	1	1	1	1	1	1	1	0	1
7	Clobazam	1	1	1	1	1	1	1	1	1
8	Clopidogrel	1	1	0	1	1	0	1	0	1
9	Clozapine	1	1	1	1	1	1	1	0	0
10	Codeine	1	1	1	1	1	1	1	1	0
11	Dabigatran	0	1	0	0	0	0	1	0	0
12	Diazepam	1	1	1	1	1	1	1	1	1
13	Docetaxel	0	0	0	1	1	0	1	0	0
14	Flecainide	0	0	0	1	1	0	1	0	0
15	Fluvastatin	0	0	0	1	1	1	1	0	0
16	Indinavir	1	1	1	1	1	1	1	0	0
17	Irinotecan	0	0	0	1	1	0	1	0	0
18	Metoprolol	0	0	0	1	1	1	1	0	0
19	Morphine	1	1	1	1	1	1	1	1	0
20	Omeprazole	1	1	0	1	1	1	1	0	1
21	Oxycodone	1	1	1	1	1	1	1	1	0
22	Phenytoin	1	1	1	1	1	1	1	1	1
23	Pravastatin	0	0	0	0	0	1	1	0	0
24	Rosiglitazone	0	0	0	1	1	1	1	0	0
25	Rosuvastatin	0	0	0	0	0	1	1	0	0
26	Theophylline	1	1	1	1	1	1	1	1	0
27	Tizanidine	1	1	1	1	1	1	1	0	0
28	Topiramate	1	1	1	1	1	1	1	1	0
29	Warfarin	1	1	1	1	1	1	1	1	1
30	Zonisamide	0	1	0	1	1	1	1	1	0

	UpToDate	Micromedex	Medscape	WebMD	Drugs.com	DrugBank Online	Natural Medicines	Facts and Comparisons
True Positive	18	16	18	18	17	18	12	8
True Negative	10	12	4	4	4	1	11	12
False Positive	2	0	8	8	8	11	1	0
False Negative	0	2	0	0	1	0	6	10
Specificity (95% CI = LL, UL)	83.3% (51.6-97.9)	100% (73.5-100)	33.3% (9.9-65.1)	33.3% (9.9-65.1)	33.3% (9.9-65.1)	8.3% (0.2-38.5)	91.7% (61.5-99.8)	100% (73.5-100)
Sensitivity (95% CI = LL, UL)	100% (81.5-100)	88.9% (65.3-98.6)	100% (81.5-100)	100% (81.5-100)	94.4% (72.7-99.9)	100% (81.5-100)	66.7% (41.0-86.7)	44.4% (21.5-69.2)
Overall Accuracy (95% CI = LL, UL)	93.3% (77.9-99.2)	93.3% (77.9-99.2)	73.3% (54.1-87.7)	73.3% (54.1-87.7)	70% (50.6-85.3)	63.3% (43.9-80.1)	76.7% (57.7-90.1)	66.7% (47.2-82.7)

Table 2. *Testing individual DISPs with 30 unique drug-cannabis interactions for specificity and sensitivity. Each "1" represents that the DISP flagged the DDI pair while each "0" represents that the DDI pair was not flagged by the DISP. Green cells represent true positives and true negatives while red cells represent false positives or false negatives. At the bottom of the table, each true positive/negative and false positive/negative was tallied. Using IBM SPSS Statistics Data Editor, results were calculated for specificity, sensitivity, and overall accuracy with individual 95% confidence intervals.*

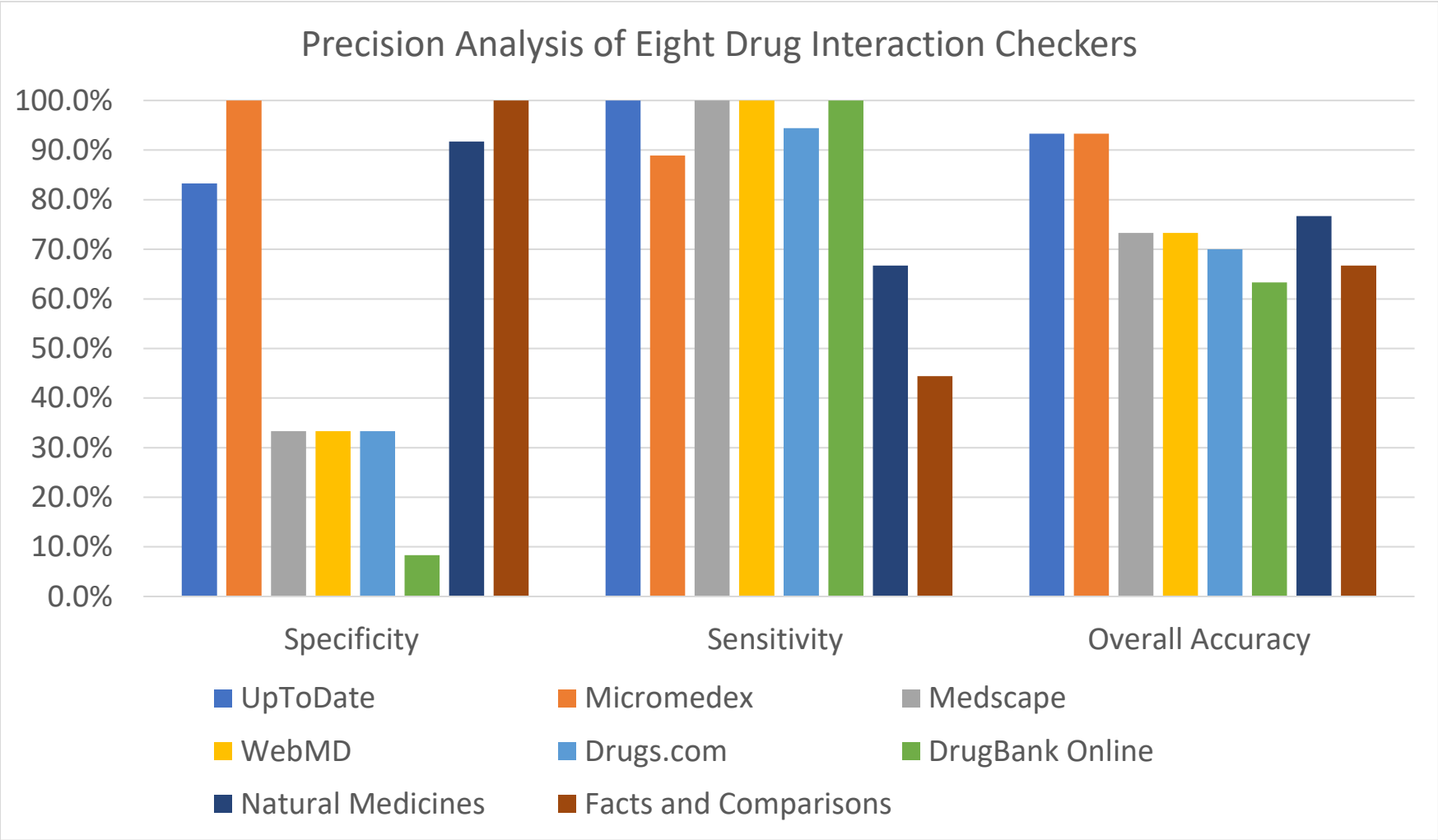

Figure 1. *Precision analysis of eight DISPs, categorized by specificity, sensitivity, and overall accuracy.*

3a. Creating a literature review table

The results for the literature review table are listed in Table 1. A total of 30 DDI pairs were included from the literature. There were 18 "true" DDI pairs and 12 "false" DDI pairs. "False" DDI pairs were further categorized into being "theoretical but proven false" (n=4) or "randomly generated" (n=8). The basis to qualify a DDI as clinically significant was based on the type of study and level of evidence each study held which was derived from the Centre for Evidence-Based Medicine's "Levels of Evidence for Therapeutic Studies", which can be defined using the criteria in the label for Table 1.[10]

3b. Evaluating individual DISPs

The results for evaluation of each individual DISP is shown in Table 2. The DISPs that were chosen were from the following companies: UpToDate, Micromedex, Natural Medicines, and Facts and Comparisons, DrugBank Online, Drugs.com, WebMD, and Medscape. The first four DISPs are generally intended for healthcare professionals while the second four are intended for layperson use. As seen in Table 2, some DISPs had notably more red cells than others which signified less overall accuracy.

3c. Sensitivity, Specificity, Overall Accuracy, and Inter-Rater Reliability

Results for statistics are shown in Table 2 and Figure 1. Overall Fleiss' kappa score, which measured inter-rater reliability and how well the DISPs agreed with each other, was somewhat poor (k = 0.216, [95% CI = 0.148, 0.284]). Scores for sensitivity, specificity, and overall accuracy were calculated and reported in Table 2 and Figure 1. Overall, the worst offenders for specificity were WebMD (33.3%), Drugs.com (33.3%), Medscape (33.3%), and DrugBank Online (8.3%). For sensitivity, the lowest performing DISPs were Natural Medicines (66.7%) and Facts and Comparisons (66.7%). For overall accuracy, Facts and Comparisons (66.7%) and DrugBank Online (63.3%) scored lowest.

4.Discussion

To begin with the literature review table (Table 1), the drug interaction pairs had been generated from existing literature and were included if they were considered "clinically significant". Because there was only one reviewer for the creation of this table, the definition for what was "clinically significant" may drastically vary from other healthcare professionals. A DDI was determined in this case to be "clinically significant" if there was literature to support evidence that an interaction with cannabis resulted in higher/lower levels of the drug and that it caused and adverse drug event. Many different therapeutic classes (oncology, neurology, etc.) of drugs were included in an attempt to diversify results. A relatively low number of DDIs were captured (n=30) which may contribute to wider confidence intervals for scores of sensitivity/specificity/accuracy. Only DDIs that affected serum levels/ADEs with prescription drug were included in the table and DDIs that affected serum levels of cannabis were excluded.

Next, when evaluating individual DISPs, only eight programs were included due to lack of accessibility (i.e., subscription costs). DISPs were evaluated whether they reported any interaction with cannabis and a prescription drug that was included in Table 1. When using the search terms "cannabis, cannabidiol, dronabinol", some programs (Facts and Comparisons) would not include "cannabis", which is a major deficit for its overall accuracy of detecting DDIs. Programs also varied widely in the management of DDIs. For example, UpToDate describes the interaction, cites multiple sources, and then describes in detail how to manage the interaction while other programs like WebMD or Medscape may not cite literature and simply flag whether or not there could be a DDI.

For sensitivity, specificity, overall accuracy, and inter-rater reliability, scores generally affirmed that there is not great consensus on what defines a DDI with cannabis and prescription drugs. A Fleiss' kappa score of k=0.216 is generally interpreted as slight to fair agreement, although there is no

universally accepted interpretation. Even more, many DISPs do not hold great predictive value for detecting DDIs between cannabis and prescription drugs, which may lead to patient harm. In general, programs that are tailored to healthcare professionals outperformed programs that are meant for the layperson. Surprisingly, one DISP (Facts and Comparisons), which is meant for use by pharmacists, scored second to lowest overall in terms of accuracy. When the layperson uses commercial DISPs that are found online, it should be noted that there are severe limitations to detecting clinically significant DDIs and that healthcare professionals should be consulted when making decisions on therapy.

There were several limitations to this study. First, although there was meant to be a strong objective approach in creating the literature review table, the use of one author limits the use of the table. DDIs that were considered "clinically significant" were included if the literature supported the decision, but other healthcare professionals may agree or disagree on the definition as to what constitutes a DDI. Next, drug interactions with cannabis are very different from normal interactions in that many users do not ingest cannabis every day, which results in variable interactions. Also, the route of which cannabis is consumed varies wildly and thus so do the absorption and pharmacokinetics. Even more, when CBD is being considered as a DDI, it is generally dosed in much larger quantities than when taken with cannabis and thus DDIs with CBD may not be relevant to cannabis. Lastly, the number of DDIs in Table 1 is somewhat low, which resulted in wide confidence intervals for the accuracy scores.

5.Conclusions

Healthcare professionals and laypersons who utilize programs to detect DDIs should practice caution when attempting find interactions between cannabis and prescription drugs. Programs that cite literature and have high specificity/sensitivity/overall accuracy (UpToDate, Micromedex) should be used but only with aid of a healthcare professional. Future clinical research is needed to explore clinically significant drug interactions with cannabis. Additionally, both healthcare professionals and laypersons should receive more education on the drug interactions with cannabis and how it may affect healthcare.

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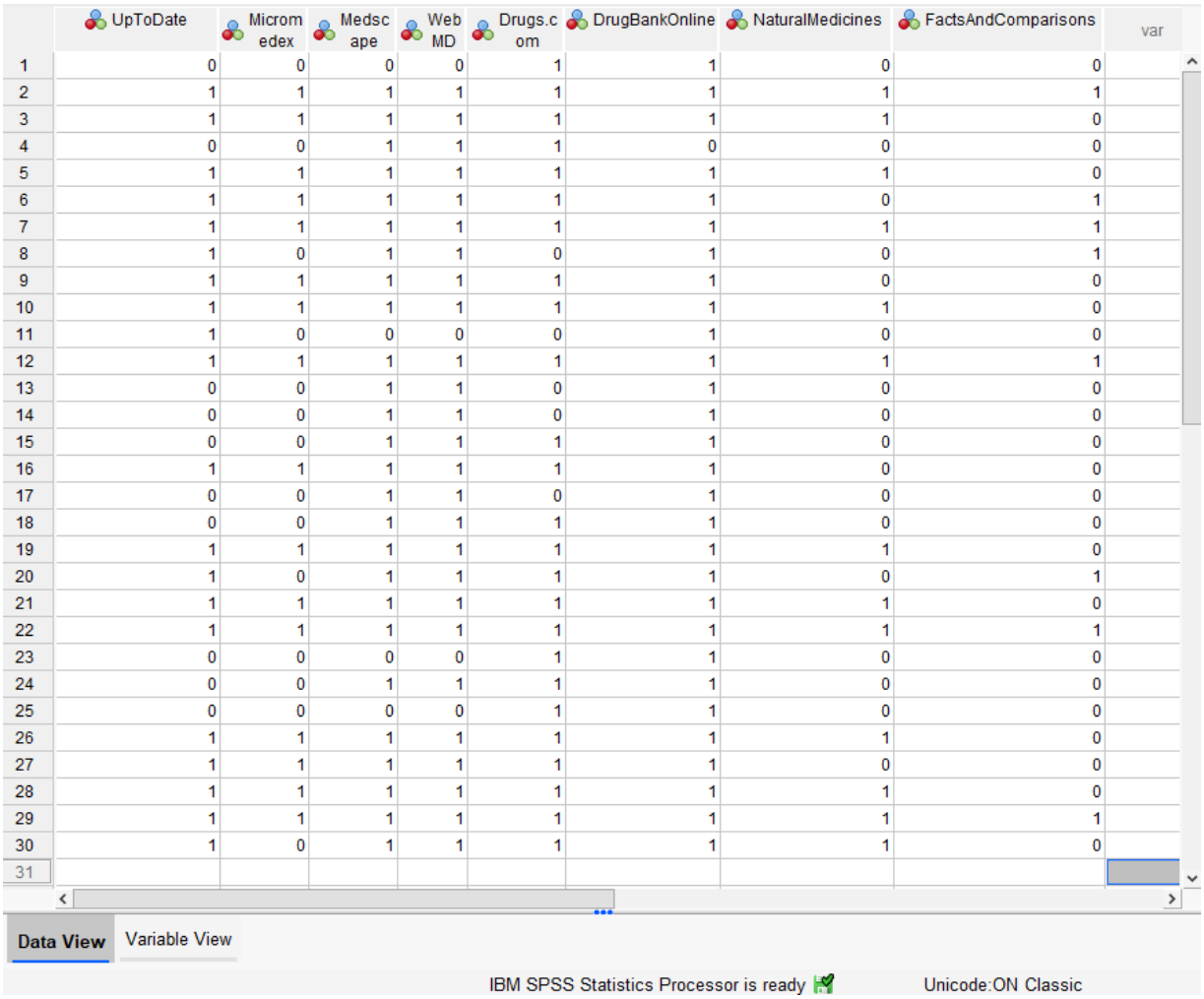
Supplementary Information - Data Captured from IBM SPSS



	UpToDate	Micromedex	Medscape	WebMD	Drugs.com	DrugBankOnline	NaturalMedicines	FactsAndComparisons	var
1	0	0	0	0	1	1	0	0	
2	1	1	1	1	1	1	1	1	
3	1	1	1	1	1	1	1	0	
4	0	0	1	1	1	0	0	0	
5	1	1	1	1	1	1	1	0	
6	1	1	1	1	1	1	0	1	
7	1	1	1	1	1	1	1	1	
8	1	0	1	1	0	1	0	1	
9	1	1	1	1	1	1	0	0	
10	1	1	1	1	1	1	1	0	
11	1	0	0	0	0	1	0	0	
12	1	1	1	1	1	1	1	1	
13	0	0	1	1	0	1	0	0	
14	0	0	1	1	0	1	0	0	
15	0	0	1	1	1	1	0	0	
16	1	1	1	1	1	1	0	0	
17	0	0	1	1	0	1	0	0	
18	0	0	1	1	1	1	0	0	
19	1	1	1	1	1	1	1	0	
20	1	0	1	1	1	1	0	1	
21	1	1	1	1	1	1	1	0	
22	1	1	1	1	1	1	1	1	
23	0	0	0	0	1	1	0	0	
24	0	0	1	1	1	1	0	0	
25	0	0	0	0	1	1	0	0	
26	1	1	1	1	1	1	1	0	
27	1	1	1	1	1	1	0	0	
28	1	1	1	1	1	1	1	0	
29	1	1	1	1	1	1	1	1	
30	1	0	1	1	1	1	1	0	
31									

Fleiss Multirater Kappa

Overall Agreement[a]

	Kappa	Asymptotic Standard Error	Asymptotic z	Asymptotic Sig.	Asymptotic 95% Confidence Interval Lower Bound	Asymptotic 95% Confidence Interval Upper Bound
Overall Agreement	.216	.035	6.260	<.001	.148	.284

a. Sample data contains 30 effective subjects and 8 raters.

UpToDate * GoldStandard Crosstabulation

			GoldStandard		
			0	1	Total
UpToDate	0	Count	10	0	10
		% within GoldStandard	83.3%	0.0%	33.3%
	1	Count	2	18	20
		% within GoldStandard	16.7%	100.0%	66.7%
Total		Count	12	18	30
		% within GoldStandard	100.0%	100.0%	100.0%

Micromedex * GoldStandard Crosstabulation

			GoldStandard		
			0	1	Total
Micromedex	0	Count	12	2	14
		% within GoldStandard	100.0%	11.1%	46.7%
	1	Count	0	16	16
		% within GoldStandard	0.0%	88.9%	53.3%
Total		Count	12	18	30
		% within GoldStandard	100.0%	100.0%	100.0%

Medscape * GoldStandard Crosstabulation

			GoldStandard		
			0	1	Total
Medscape	0	Count	4	0	4
		% within GoldStandard	33.3%	0.0%	13.3%
	1	Count	8	18	26
		% within GoldStandard	66.7%	100.0%	86.7%
Total		Count	12	18	30
		% within GoldStandard	100.0%	100.0%	100.0%

WebMD * GoldStandard Crosstabulation

			GoldStandard	Total

			0	1	
WebMD	0	Count	4	0	4
		% within GoldStandard	33.3%	0.0%	13.3%
	1	Count	8	18	26
		% within GoldStandard	66.7%	100.0%	86.7%
Total		Count	12	18	30
		% within GoldStandard	100.0%	100.0%	100.0%

Drugs.com * GoldStandard Crosstabulation

			GoldStandard		
			0	1	Total
Drugs.com	0	Count	4	1	5
		% within GoldStandard	33.3%	5.6%	16.7%
	1	Count	8	17	25
		% within GoldStandard	66.7%	94.4%	83.3%
Total		Count	12	18	30
		% within GoldStandard	100.0%	100.0%	100.0%

DrugBankOnline * GoldStandard Crosstabulation

			GoldStandard		
			0	1	Total
DrugBankOnline	0	Count	1	0	1
		% within GoldStandard	8.3%	0.0%	3.3%
	1	Count	11	18	29
		% within GoldStandard	91.7%	100.0%	96.7%
Total		Count	12	18	30
		% within GoldStandard	100.0%	100.0%	100.0%

NaturalMedicines * GoldStandard Crosstabulation

			GoldStandard		
			0	1	Total
NaturalMedicines	0	Count	11	6	17
		% within GoldStandard	91.7%	33.3%	56.7%
	1	Count	1	12	13
		% within GoldStandard	8.3%	66.7%	43.3%
Total		Count	12	18	30
		% within GoldStandard	100.0%	100.0%	100.0%

FactsAndComparisons * GoldStandard Crosstabulation

			GoldStandard		
			0	1	Total
FactsAndComparisons	0	Count	12	10	22
		% within GoldStandard	100.0%	55.6%	73.3%
	1	Count	0	8	8
		% within GoldStandard	0.0%	44.4%	26.7%
Total		Count	12	18	30
		% within GoldStandard	100.0%	100.0%	100.0%